The electrochemical oxidation of some 4-benzyltetrahydroisoquinolines.

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THE ELECTROCHEMICAL OXIDATION OF SOME 4-BENZYLTETRAHYDROISOQUINOLINES

Submitted by

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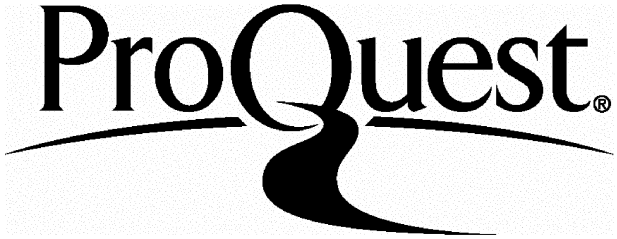
for the degree of

Doctor of Philosophy

of the University of Bath

1980

M. P. Carmody



PREFACE

The author wishes to express his thanks to Dr. Malcolm Sainsbury for his interest and guidance throughout the course of the work, to to Dr. R.F. Newton of Glaxo Group Research and to the technical staff of the Chemistry Department of the University of Bath.

The award of a Research Studentship by the Science Research Council is most gratefully acknowledged.

ABSTRACT

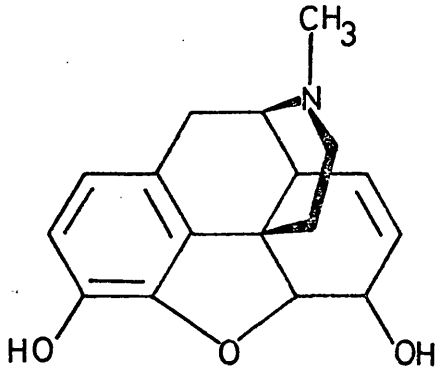
The cyclisation of N-methyl-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide and related structures does not yield 6,7-dimethoxy-4-(3,4-dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydro-3-isoquinoline, but gives instead dibenzo[b,f]cycloheptane derivatives. Anodic oxidation of 6,7-dimethoxy-4-(3,4-dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline affords the corresponding 3,4-dihydroisoquinolinium and 4-(3,4-dimethoxybenzylidene)-6,7-dimethoxy-2-methyl-1,4-dihydroisoquinolinium salts. No intramolecularly aryl-aryl coupled products are isolated. 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxyphenyl)isoquinoline was synthesised and its electrochemistry investigated.

This work was carried out in a period of 2 years, from 1977-1979.

CONTENTS

INTRODUCTION

"Among the remedies which it has pleased Almighty God to give man to relieve his sufferings, none is so universal and so efficacious as opium." These words were written in 1680 by Thomas Sydenham, an English physician. Since that time the medical profession have tempered their admiration of the analgetic effects of the drug with a growing awareness of its toxic and addictive properties.

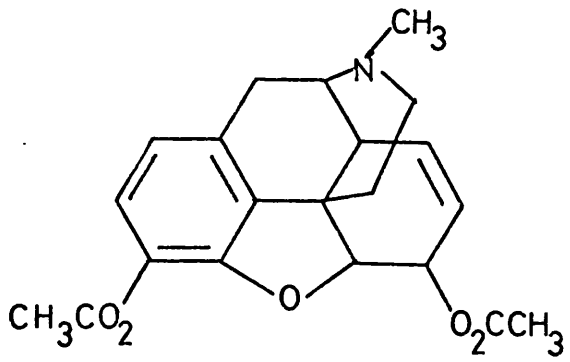


(1)

Opium, the crude dried sap of the poppy, Papaver somniferum, has been used as a drug since ancient times not only because of its analgetic properties but also because it gives rise to euphoria. In 1803 a German pharmacist Friedrich Serturner isolated the principal active constituent of opium which he called morphine (1) after Morpheus the Greek god of dreams.

The use of pure morphine rather than crude opium was thus made possible and, by the middle of the 19th century this practice was widespread. It was not until some time later that the toxicity and addictiveness of the drug

became evident. The administration of opiates to soldiers wounded in the American Civil War made addiction a significant social problem in the United States and prompted the search for non-addictive synthetic analgetics. This search has not yet been successful and several synthetic opiates at first thought to be free of their deleterious side effect have been shown subsequently to be addictive. In the 1890's, for example, the Bayer company introduced heroin(2), the diacetyl derivative of morphine, as a supposedly non-addictive analgetic. Similarly in the 1940's meperidine(3) became a very popular analgetic in the United States and it was only after some years that the growing number of meperidine addicts forced the Bureau of Narcotics to act against the continued use of the drug.



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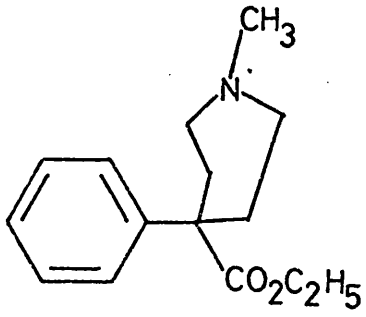
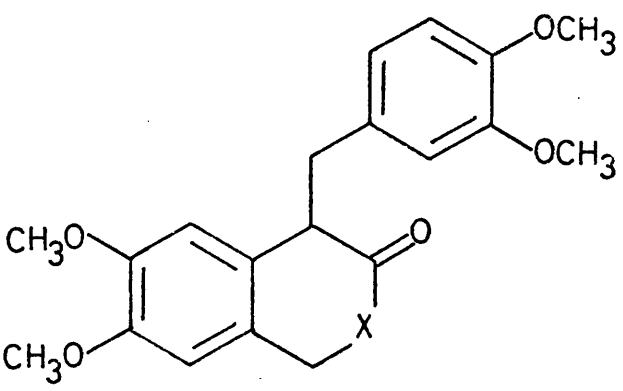
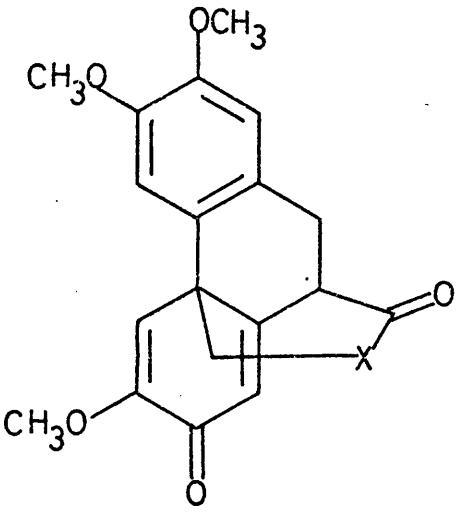


(3)

In 1972 Sainsbury and Schinazi[1] oxidised 6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-3-isochromanone(4a) at a potential of 1.1v versus the standard calomel electrode(SCE)[2]. The product they obtained (5a) is interesting because if the oxygen atom in the lactone ring was replaced by nitrogen (as N-H or N-alkyl) the compound becomes an isomorphinan analogous to AH8649 (7)[3] a non-narcotic analgetic.

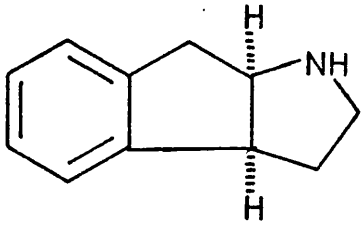


(4)a) X = O
b) X = NCH$_3$



(5)a) X = O
b) X = NCH$_3$

The related drug, AH6812(6)[4], which has the basic unit of morphine is, however, narcotic. More particularly there is an obvious relationship between the isomorphinan (5b) and levorphanol (8)[5] an effective anagetic, although narcotic, drug. The synthesis of a related structure from the cyclised lactone (5a) did not appear to present too much of a challenge but Sainsbury et al.[1] were unable to effect the substituion of oxygen by an N-methyl group by treatment with methylamine. Opening of the heterocyclic ring with elimination of formaldehyde led to formation of the dihydro anthracene derivative (9).



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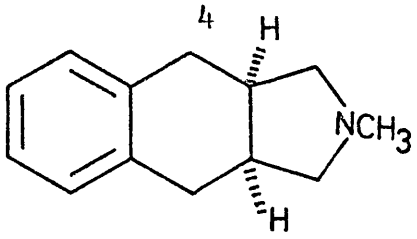

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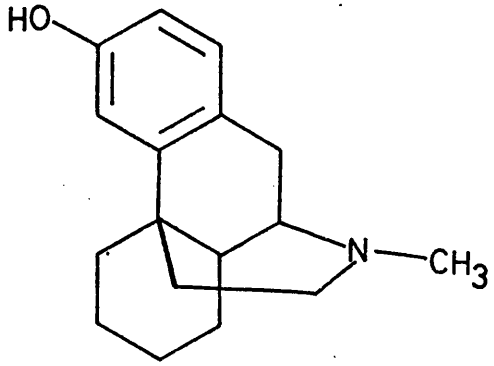
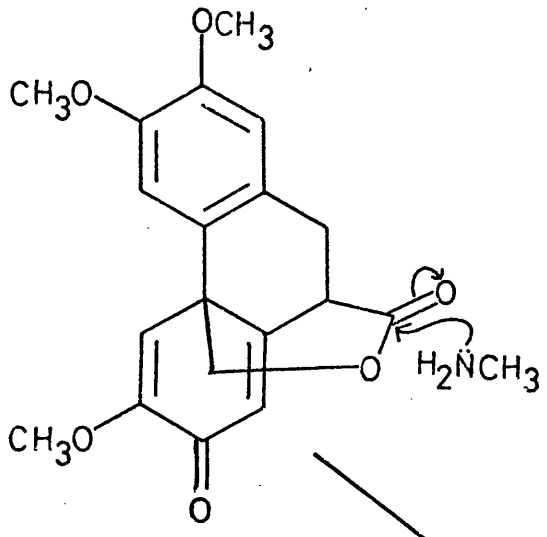


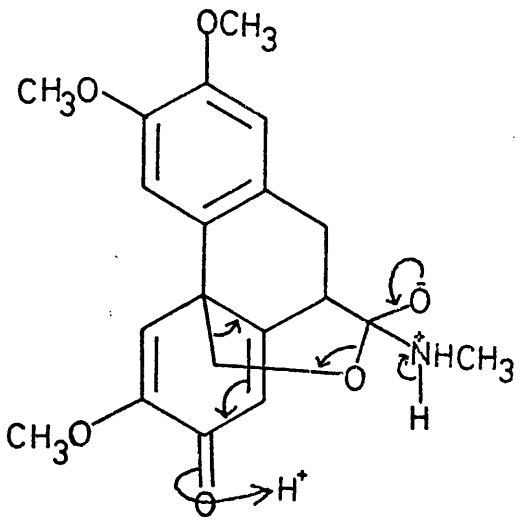
(8)

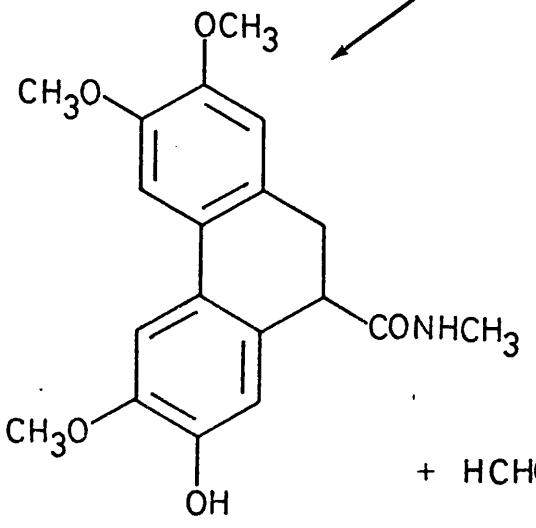
With this in mind it was decided to investigate the possibility that the 1,4-dihydro-3(2H)-isoquinolinone (4b) corresponding to the isochromanone (4a) could be converted directly into the isomorphinone (5b). This investigation forms the main theme of the research presented in this thesis.

In the electro-oxidation of oxygen bearing ring structures such as (1a) the presence of the ester group may not be necessary as the ester function itself has a relatively high oxidation potential, however in the case of the isoquinolinone (4b) the ester unit is replaced by an amido group. Here the carbonyl group would appear to be very important since the lone pair electrons of an amine are easily oxidised at potentials of ca. 0·5V versus SCE[6], compared with ca. 1·1V which is the potential necessary for oxidation of the aryl rings. In other words it seems probable that an



(5a)

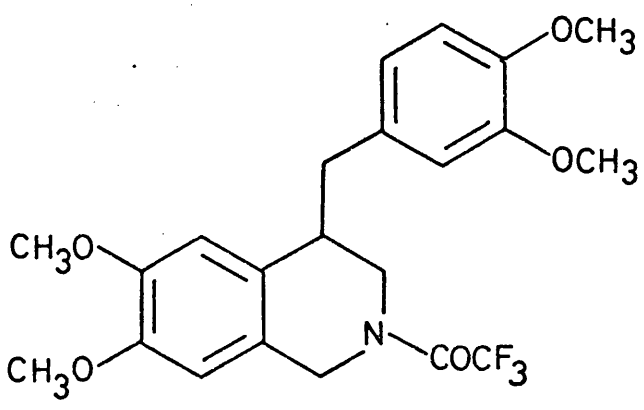




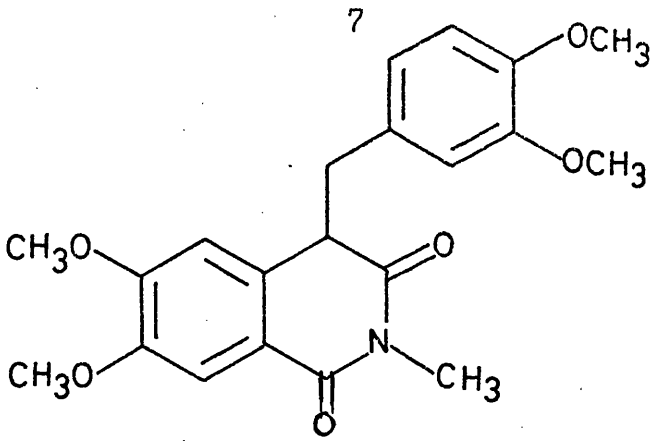
+ HCHO

(9)

attempt to oxidise a 4-benzyltetrahydroisoquinoline will lead to products arising from radical cations formed at the basic nitrogen atom,(for a discussion of the electrochemical oxidation of the 1-benzyl analogues see page 94). On the other hand the oxidation of a tertiary amide nitrogen takes place at a potential much greater than that necessary to oxidise the aryl rings[7]. Direct aryl-aryl coupling is then possible. On this basis it was considered that the electrochemical oxidation of the tetrahydroisoquinoline(10) and of the isoquinolinedione (11) should also be investigated. In the latter case there is the additional problem of the presence of a carbonyl group in conjugation with an aryl ring. This raises the oxidation potential of that ring and is therefore likely to increase the proportion of intramolecular coupling <u>via</u> the benzyl substituent. Since it may be possible to control the proportion of intramolecularly coupled product formed it is possible that an isomorphinone will be the major product.



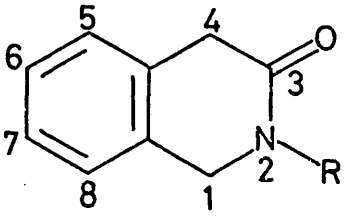
(10)



(11)

Before going on to discuss the work done towards achieving the synthesis of an isomorphinone derivative consideration will be given to the general methods available for the synthesis of 3(2H)-isoquinolinones, 1,3-isoquinolinediones and 1,2,3,4-tetrahydroisoquinolines and also the principal theories of the mechanism of aryl-aryl electrochemical oxidative coupling.

The Synthesis of 1,4-dihydro-3(2H)-isoquinolinones(12)

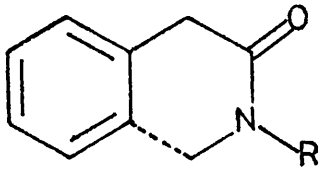


(12)

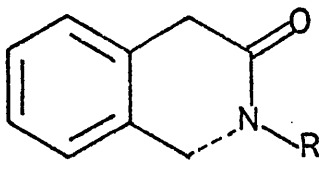
1,4-Dihydro-3(2H)-isoquinolinones are poorly represented in the literature. Compared with many other isoquinoline derivatives there are comparatively few good general methods of synthesis and such methods as there are tend to favour the preparation of 1-aryl substituted compounds. There are, however, examples of a fairly broad range of substituted compounds although the scope of the various synthetic methods

has not been fully explored.

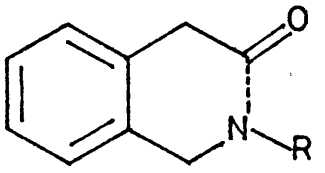
It is possible to consider the types preparations according to which bond in the heterocyclic ring system is last formed. viz:-



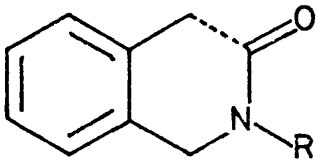
Type A



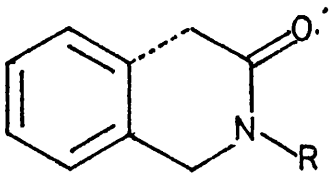
Type B



Type C



Type D

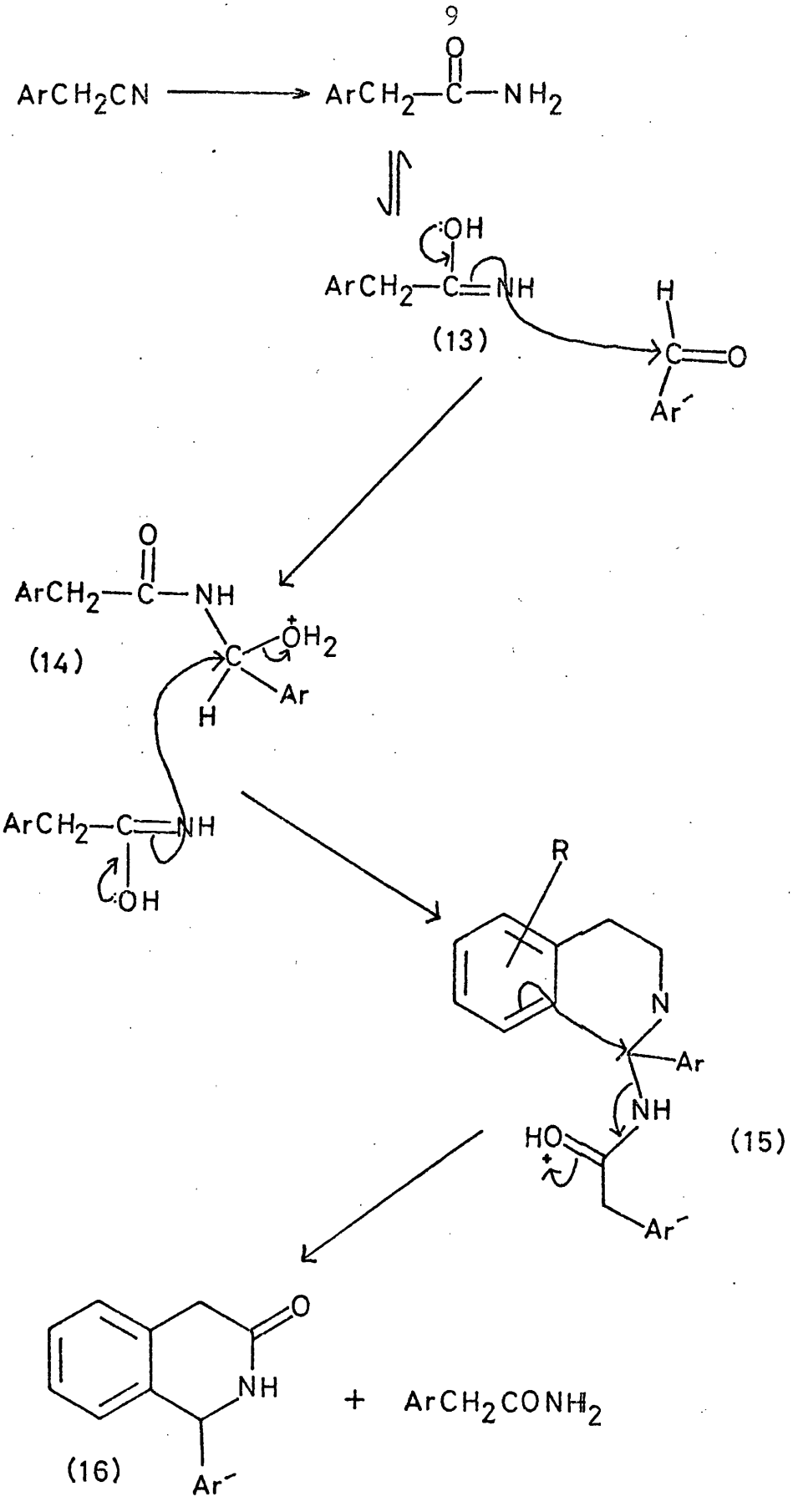


Type E

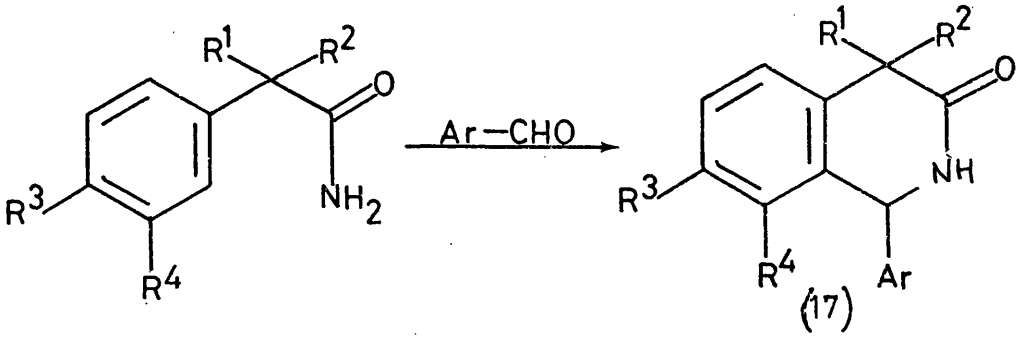
Examples are known of all types with the exception of type D, the most common being types A and E.

Type A syntheses

The usual method which is representative of this type is that of Deak[8]; this involves the reaction of one equivalent of an aromatic aldehyde with two equivalents of a benzyl nitrile in the presence of polyphosphoric acid. The initial


ArCH2CN
ArCH2—C—NH2
O
ArCH2—C=NH
OH
(13)
H
C=O
Ar
ArCH2—C—NH
O
(14)
OH2
C
Ar
H
ArCH2—C=NH
OH
R
N
Ar
NH
HO
(15)
Ar
O
NH
Ar
+ ArCH2CONH2
(16)

product is a diamide(15) which then cyclises to the isoquinolinone(16) with the formation of one equivalent of an arylacetamide. Presumably in these reactions partial hydrolysis of the nitrile to the amide occurs which acting as the tautomer(13) may then attack the carbon atom of the benzaldehyde carbonyl group. A similar reaction now upon an intermeadiate carbinol affords amides of the type(15). The manner by which the last mentioned compound cyclises is mechanistically interesting and probably involves initial protonation of the substrate followed by elimination of an arylacetamide. Deak and his co-workers demonstrated subsequently that it was possible to isolate the interme diate diamide(15) and to convert it into the isoquinolinone(16) by the action of polyphosphoric acid. They also prepared other diamides and were able to convert them into the corresponding 1,4-dihydro-3(2H)-isoquinolinones as in the case of compounds of type(17) which have been found to have anticonvulsant activity[9,10].



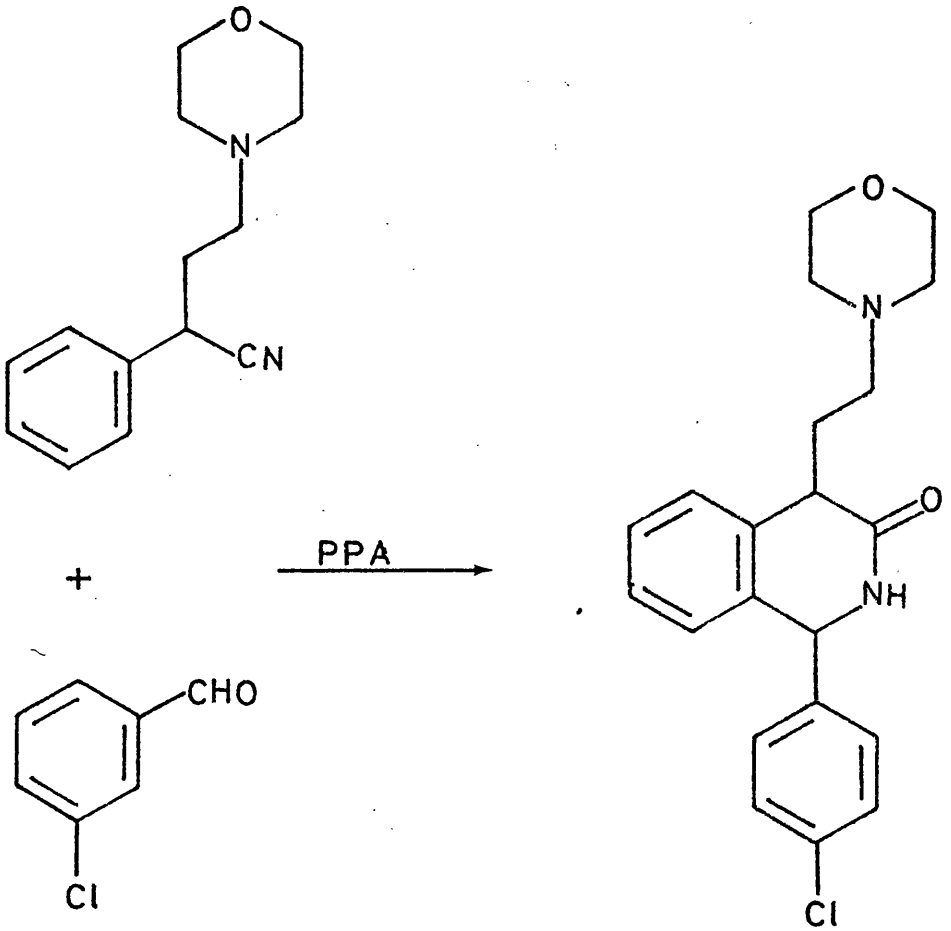
(17)

Ar= phenyl or substituted phenyl

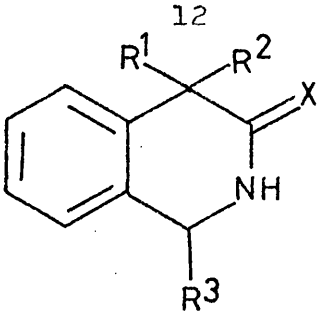
R^2, R^1= alkyl or H

R^3, R^4= methoxy or H

The cyclisation fails when deactivating functions i.e. chloro- or nitro- groups are present in the benzenoid ring[11]. Deak has extended the reaction considerably by incorporating α-substituents into the benzyl nitrile. Thus 4-substituted 1,4-dihydro-3(2H)-isoquinolinones become available[12,13]. Compound(18)is an example of an antiarhthmic agent synthesised by this method[14] and compounds of types (19)and (20), made similarly[15], show antichloesteremic and antidiabetic activity.



(18)



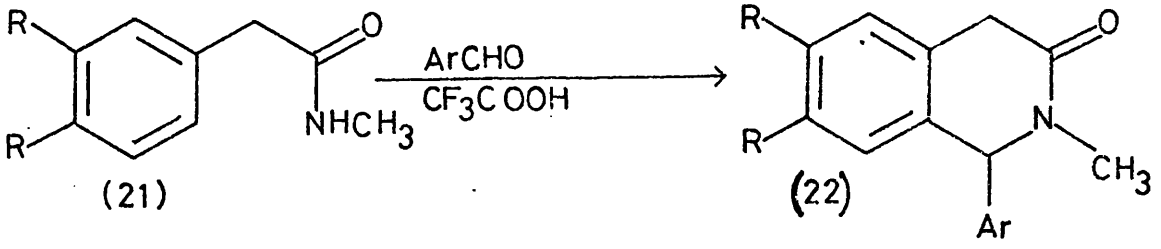
(19), X= O
(20), X= S

R^1 = H R^2 = alkyl

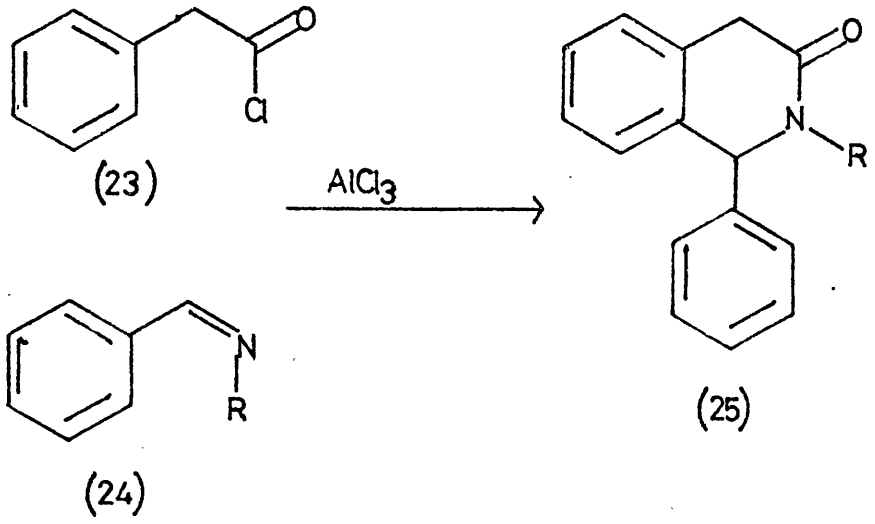
R^1 R^2 = $-(CH_2)_4-$

R^3 = phenyl or substituted phenyl

Brossi[16] has reported an analogous reaction in which a 2-substituted isoquinolinone(22) was formed by the action of trifluoroacetic acid upon mixture of an N-methyl phenylacetamide(21) and an aromatic aldehyde.

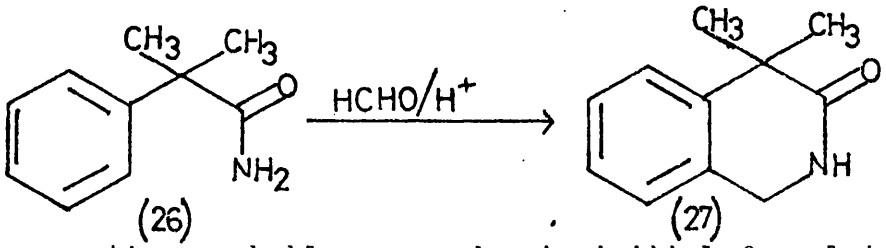


Another example of this type of synthesis is the reaction of a phenylacetyl chloride(23) with a suitable azomethine compound(24) in the presence of aluminium chloride to form a 1,4-dihydro-3(2H)-isoquinolinone(25)[17].



Type B syntheses

Only a few examples of this type of synthesis are known one of which is the treatment of a phenylacetamide(26) with formaldehyde to form the isoquinolinone(27)[18].

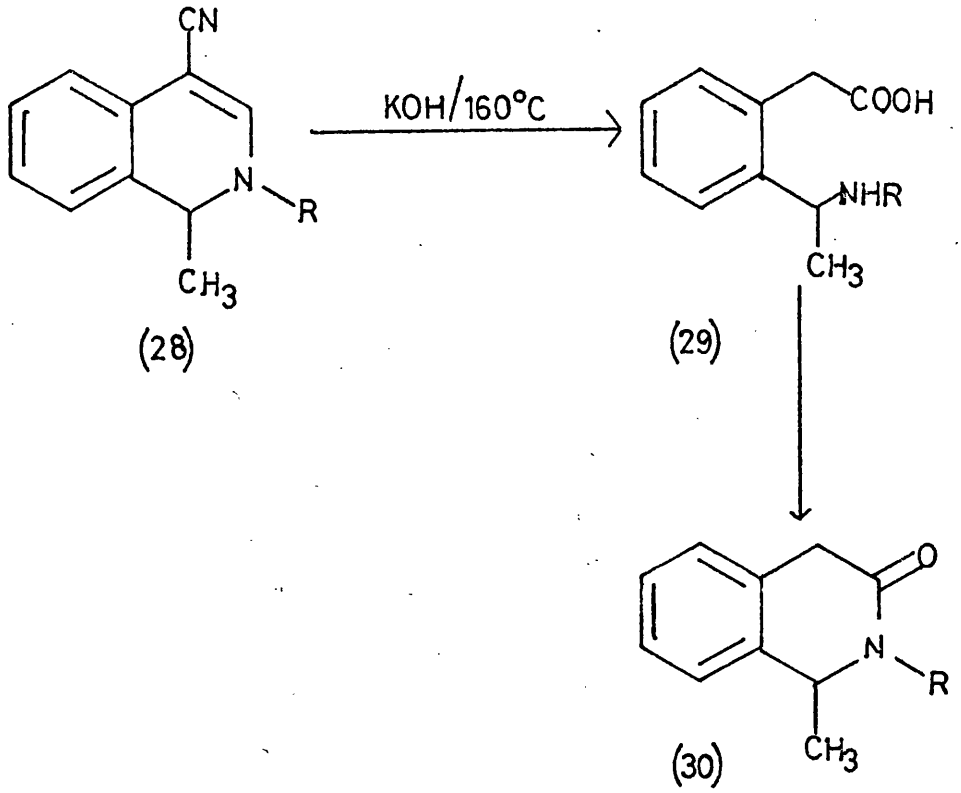


This reaction probably proceeds via initial formylation of the aryl ring followed by closure but may possibly proceed by formylation of the nitrogen followed by electrophilic attack by the aryl ring; in which case the reaction would be an example of type A.

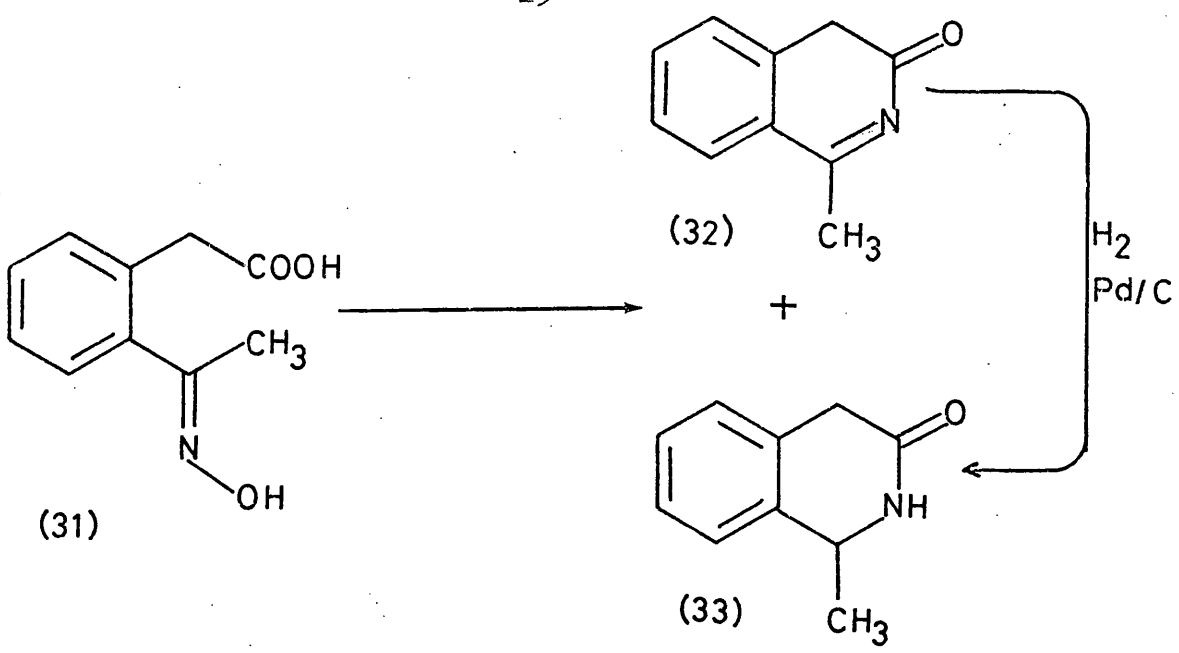
Type C syntheses

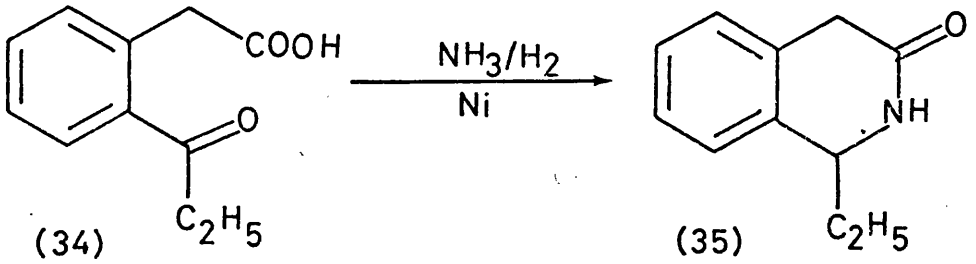
Several examples of this type of synthesis are known but none have yet been shown to be capable of general application. Natsame[19] reported a method involving the ring opening of a 4-cyano-1,2-dihydroisoquinoline(28) by treatment with

potassium hydroxide in ethane-1,2-diol at 160°C to form the acid/amine(29). This was treated with N,N-dicyclohexylcarbodiimide to form the isoquinolinone(30).



A method which may have more general application was reported by Kotake et al.[20]. Here the oxime(31) was hydrogenated over nickel to give a mixture of the isoquinolinones(32) and(33). The isoquinolinone(32)could, however be easily converted to (33)by hydrogenation over palladium on charcoal. This method was extended[21]by using the corresponding ketone as the starting material and introducing ammonia into the hydrogenation vessel. This reductive amination procedure was used, for example, to synthesise (35) from (34).

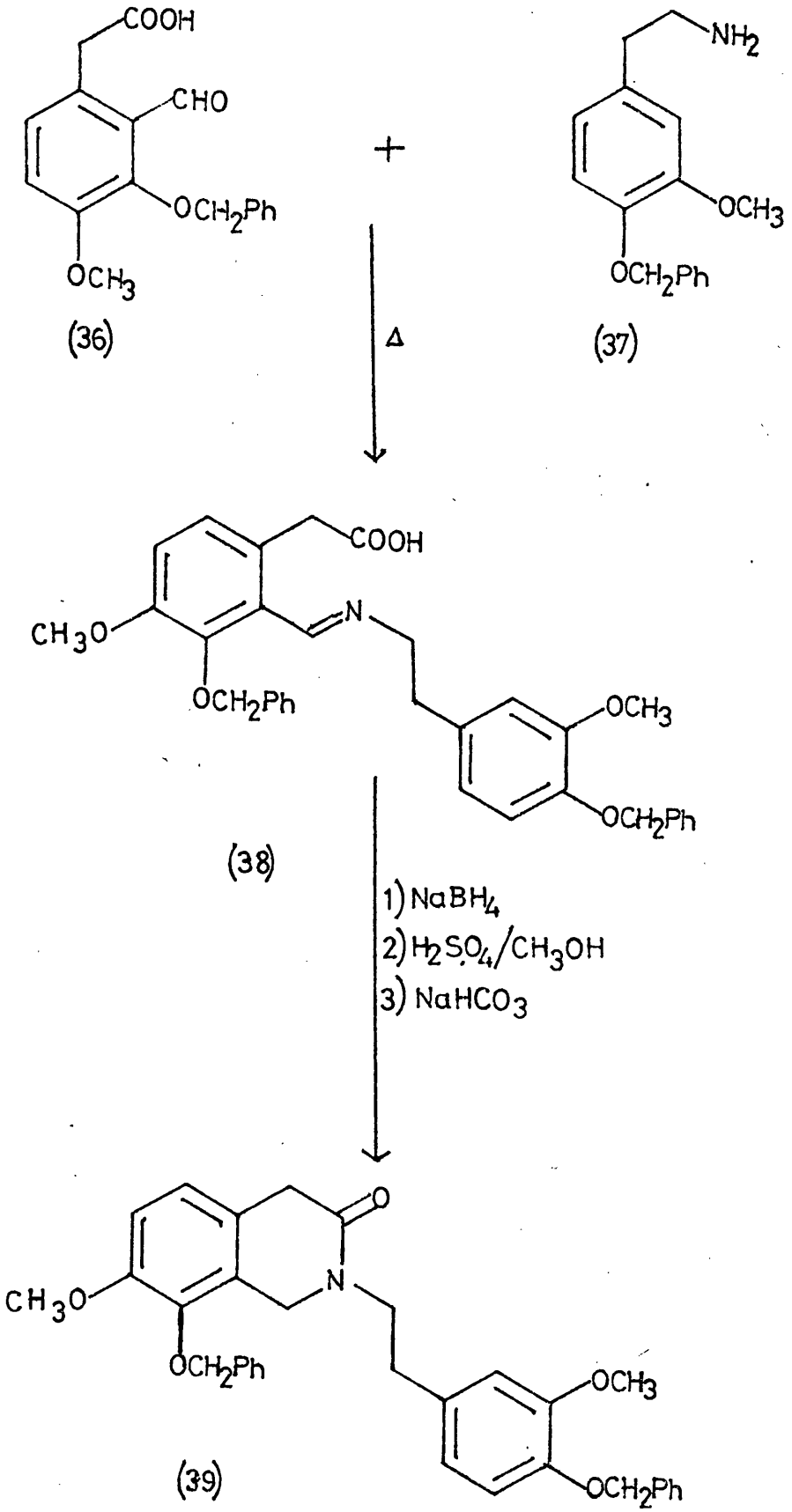


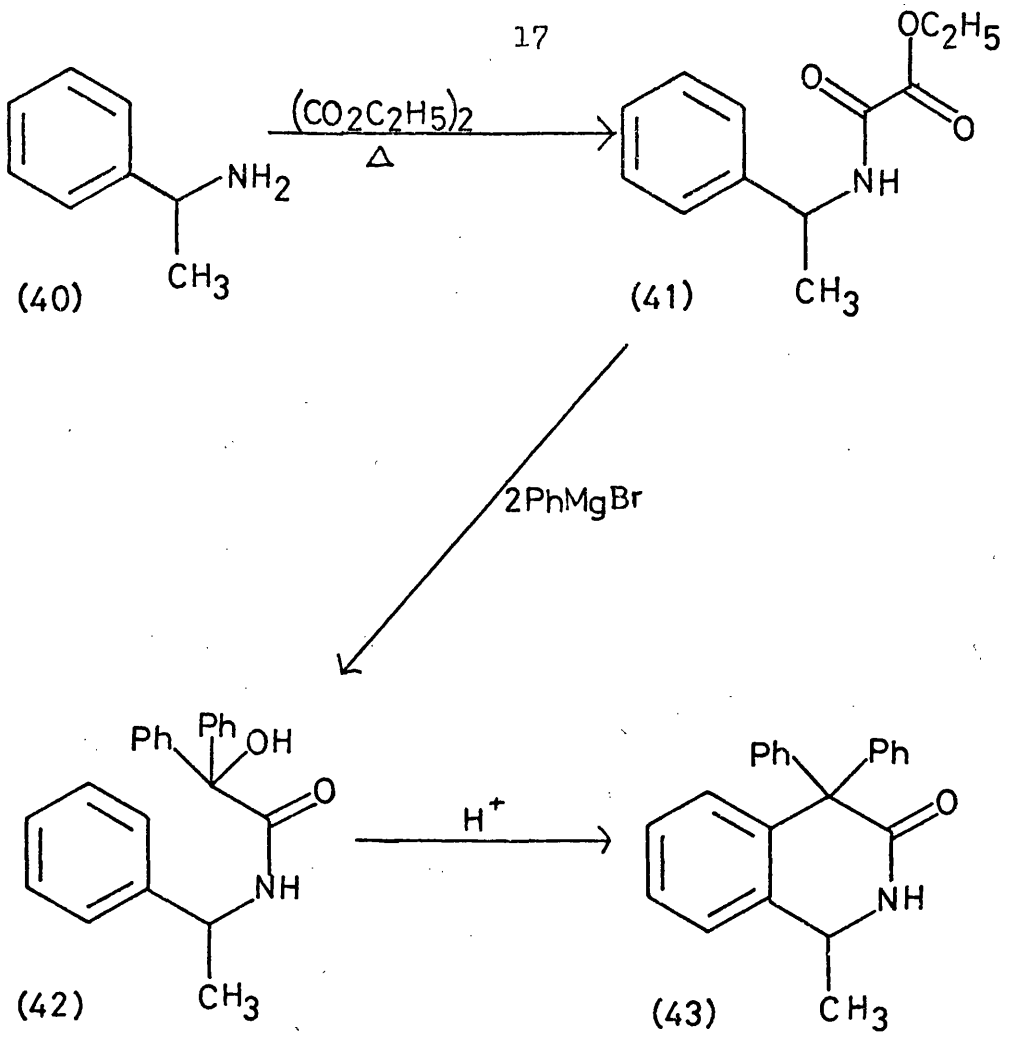


A similar sequence was employed by Battersby[22] in the synthesis of (±)-scoulerine in which (36) and (37) were used to form the imine(38) *in situ*. This compound was reduced with sodium borohydride, converted to the methyl ester and cyclised to give the isoquinolinone(39).

Type E Syntheses

The most popular of the methods of this type was first used by Petyunin in 1952[23] but is similar mechanistically to the well known Pomeranz-Fritsch reaction[24].

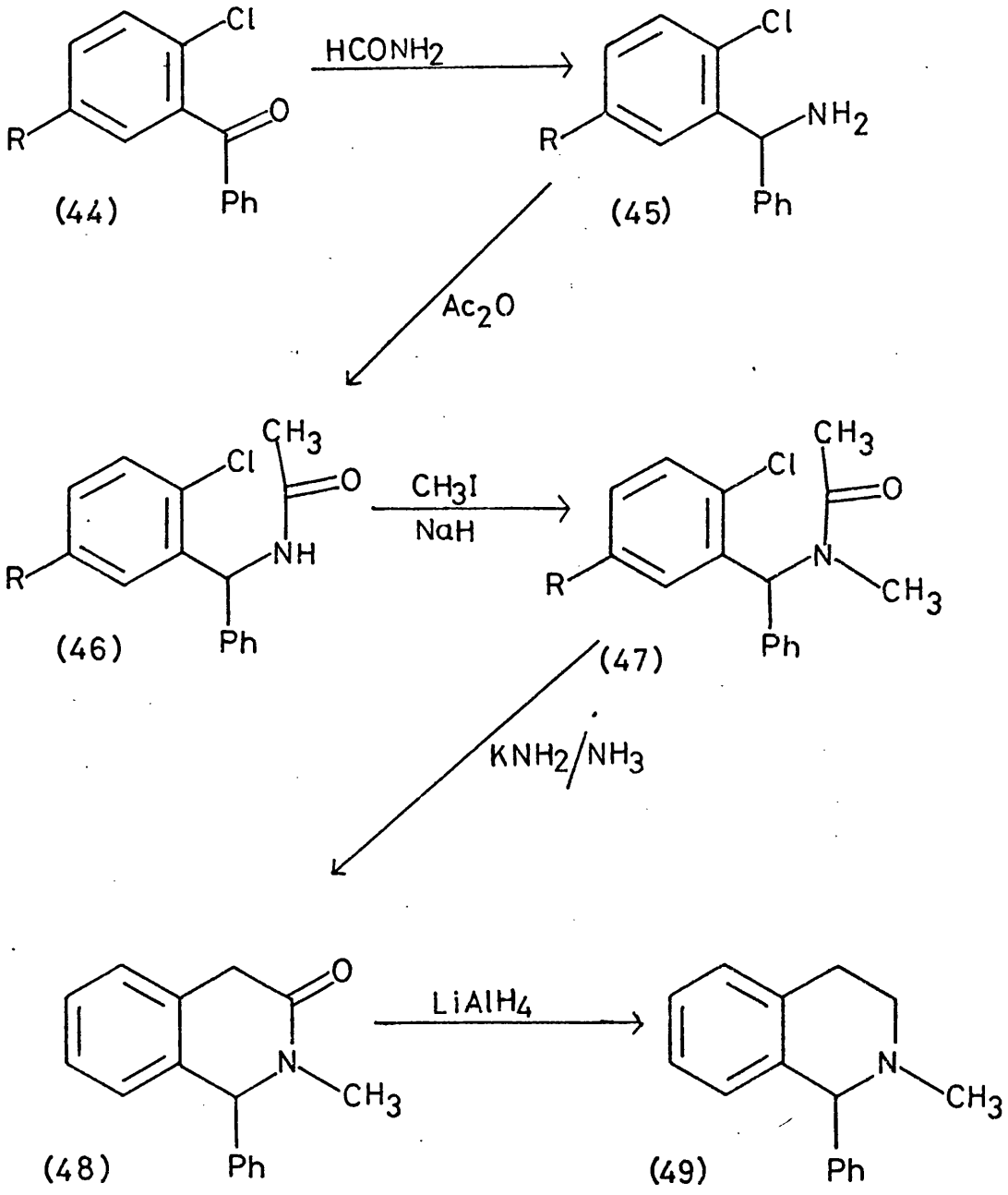

COOH
CHO
OCH2Ph
OCH3
(36)
+
NH2
OCH3
OCH2Ph
(37)
Δ
COOH
CH3O
N
OCH2Ph
OCH3
OCH2Ph
(38)
1) NaBH4
2) H2SO4/CH3OH
3) NaHCO3
O
CH3O
N
OCH2Ph
OCH3
OCH2Ph
(39)



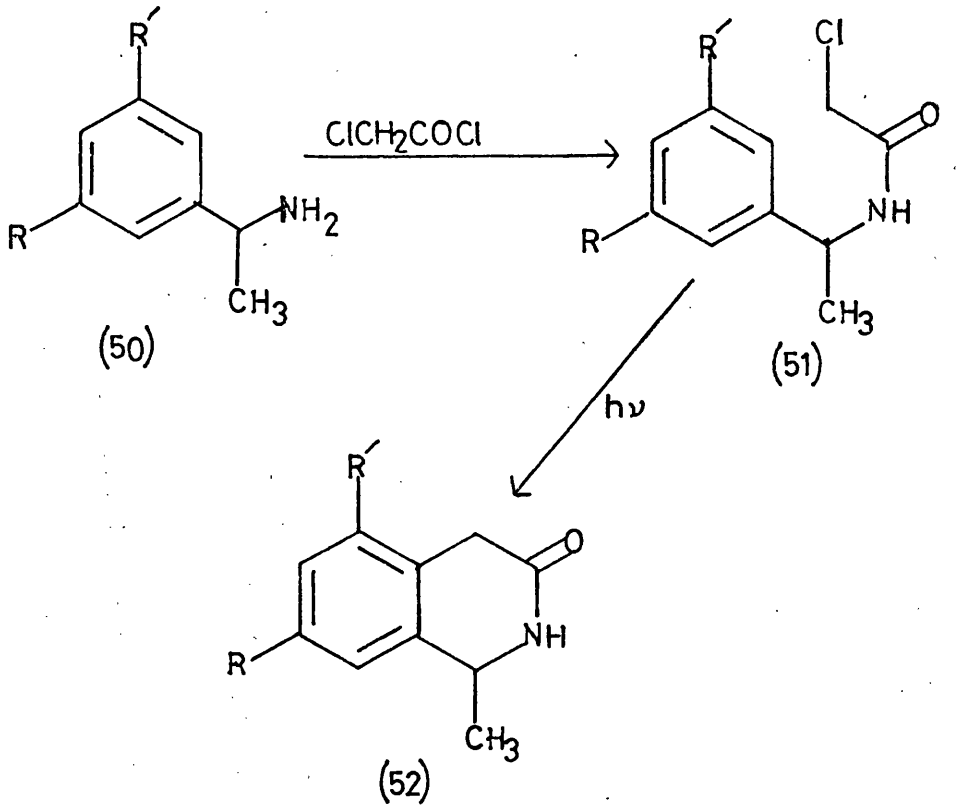
The sequence begins with the condensation of diethyl oxalate with α-methylbenzylamine(40) to form the amide(41). This is then treated with two equivalents of phenyl magnesium bromide and the resulting alcohol(42) treated with sulphuric acid to form the isoquinolinone(43), Petyunin subsequently improved and extended the method[25,26,27]. Gardent et al. used polyphosphoric acid instead of sulphuric acid[28] and Speeter[29,30] recommended an acetyl group as the leaving group in the cyclisation in place of the usual hydroxyl group.

Fryer et al.[31] selected a chloro-substituted benzophenone (44)treated it with formamide to form the amine(45) which was treated with acetic anhydride to form the secondary amide(46). This was converted to a tertiary amide(47) by

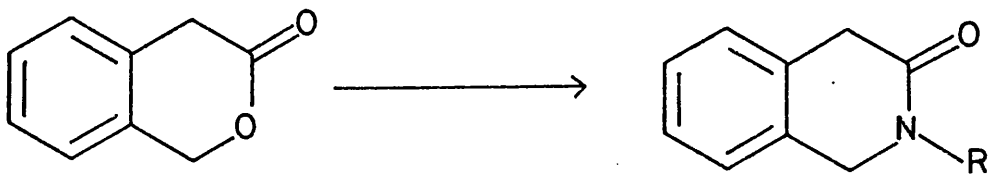
treatment with methyl iodide in the presence of sodium hydroxide. Ring closure to form the isoquinolinone(48) was effected with potassium amide in liquid ammonia. It was found that the isoquinolinone(48) could be readily reduced to the 1,2,3,4-tetrahydroisoquinoline(49) using lithium aluminium hydride.



Ikeda et al. described a method involving a photochemical ring closure[32,33] in which the amine(50) was first treated with chloroacetyl chloride to form the amide(51) which was then photochemically ring closed to form the isoquinolinone (52)



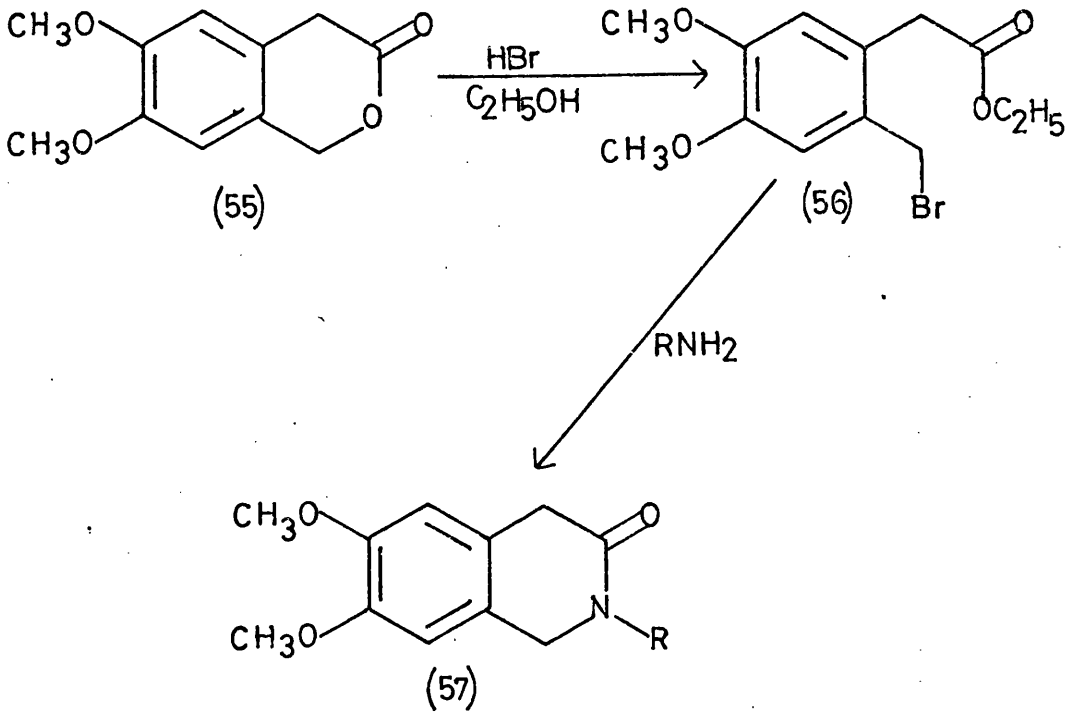
Syntheses involving conversion of a 3-isochromonone(53) to a 1,4-dihydro-3(2H)-isoquinoinone(54)



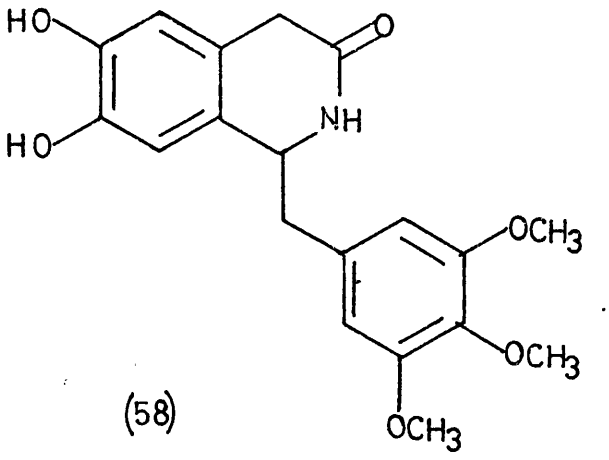
(53) (54)

There are very few reported examples of the conversion of a 3-isochromanone into a 1,4-dihydro-3(2H)-isoquinolinone and those that have been documented and are of some versatility involve quite severe conditions.

a) Conversion via an isolable intermeadiate Brossi [16] has effected this conversion by the action of an ethanolic solution of hydrogen bromide on an isochromanone(55) thus forming the bromo-ester(56) which is then treated with a primary amine to form the isoquinolinone(57).

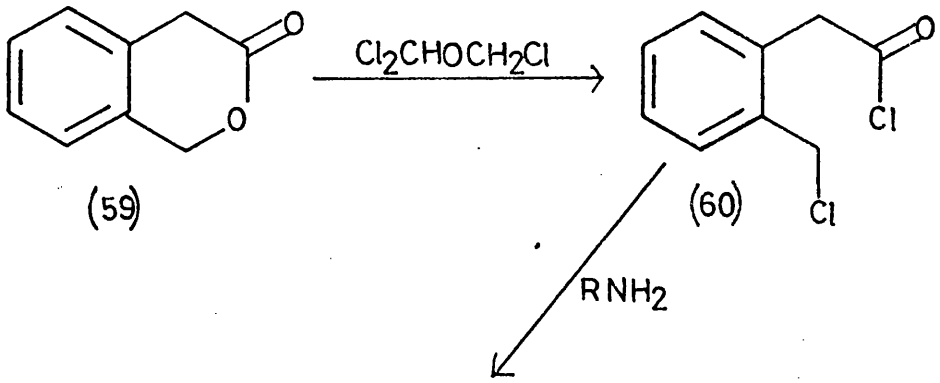


This method has also been used to prepare the 1-substituted isoquinolinone(58)[35] by the action of ammonia on the corresponding bromo-ester.



(58)

A similar method[36] involves the action of dichloromethyl-chloromethylether on the isochromanone(59) which gives the chloro-acidchloride(60). This is then heated in xylene under reflux conditions with a primary amine to form the isoquinolinone(61).

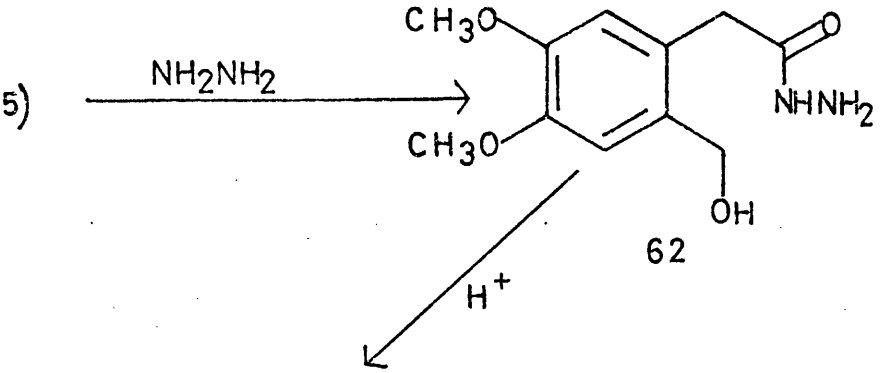


(59) (60) (61)

The only other method reported in this category[37] has as its first step the treatment of the isochromanone(55) with hydrazine hydrate to yield the hydrazide(62) which is

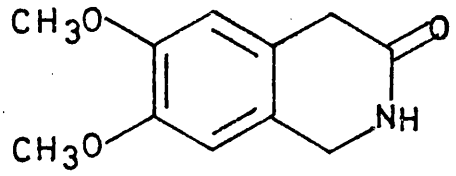
then treated with dilute hydrochloric acid to form the product(63).

(55) NH_2NH_2



62

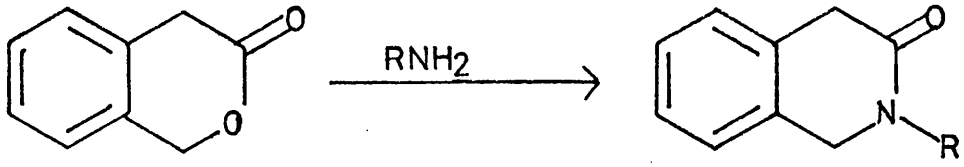
H^+



63

b) "Direct" conversions. Hoeft[36] reports three methods of "direct" conversion. The one which involves the least severe conditions being the heating under reflux conditions of a mixture of an isochromanone and a primary amine in xylene.

R= p-$CH_3C_6H_4$, 2,4,6-$(CH_3)_3C_6H_2$.



The second method consists of heating the mixture of isochromanone and amine at 210-230°C for some hours.

R= C_6H_5, p-$CH_3C_6H_4$, 2,4,6-$(CH_3)_3C_6H_2$, p-ClC_6H_4, p-$OCH_3C_6H_4$, β-napthyl.

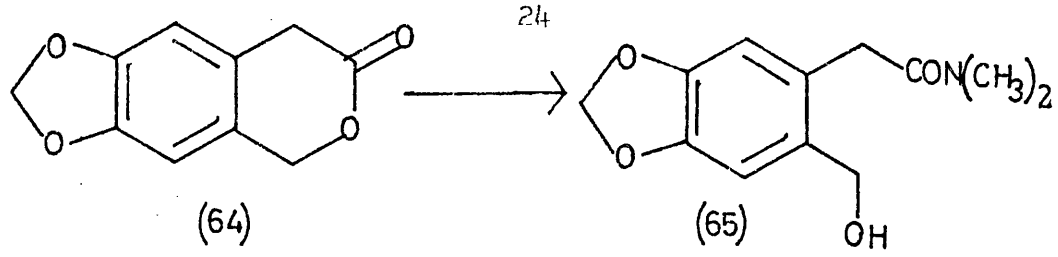
The third route is used only for the more volatile amines and requires the use of a stainless steel bomb in which a mixture of the amine and the isochromanone are heated at

220°C. R= C_6H_5, $CH_2C_6H_4$, CH_3. This method was also used by Taylor *et al.*[38] who reacted a variety of primary amines with 3-isochromanone.

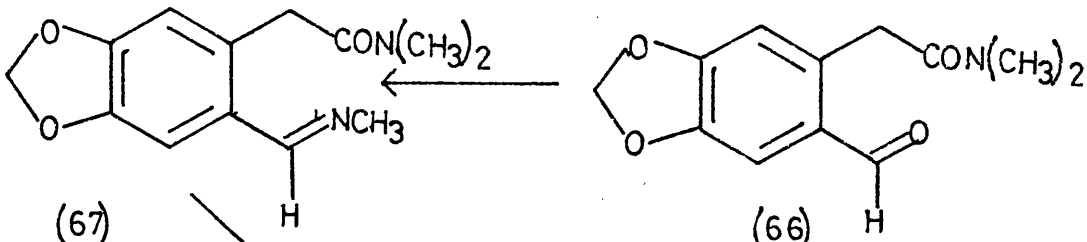
Syntheses involving the reduction of 3(2H)-isoquinolinones.

McCorkindale[39] reported the preparation of the 1,4-dihydro-3(2H)-isoquinolinone(69) and its N-H analogue. The alcohol(65) was prepared in good yield by the action of an ethanolic solution of dimethylamine on the isochromanone(64). The alcohol was subsequently oxidised by manganese dioxide in chloroform to the aldehyde(66) which was then treated with methylamine to afford the imine(67). This crude product was dissolved in hot 6M hydrochloric acid whereupon the hydrochloride(68) was formed. The free base(69) was then reduced catalytically to give, after preparative thin layer chromatography, the 1,4-dihydro analogue(70).

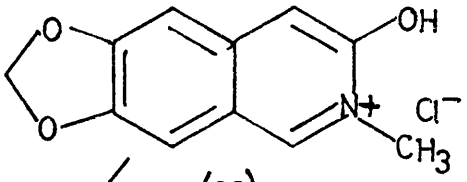
A similar reduction is reported by Elliot[40,41] in which the 1-benzylidene-substituted isochromanone(72) prepared from the acid(71) was converted to the isoquinolinone (73) by the action of methylamine at room temperature. The 3(2H)-isoquinolinone was then reduced to the 1,4-dihydro compound(74) by means of either sodium borohydride or catalytic reduction.(71) can also be converted directly to (73) by treament with ammonium acetate in acetic acid.



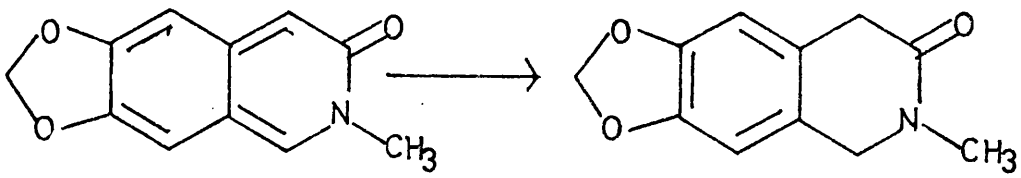
(64) (65)



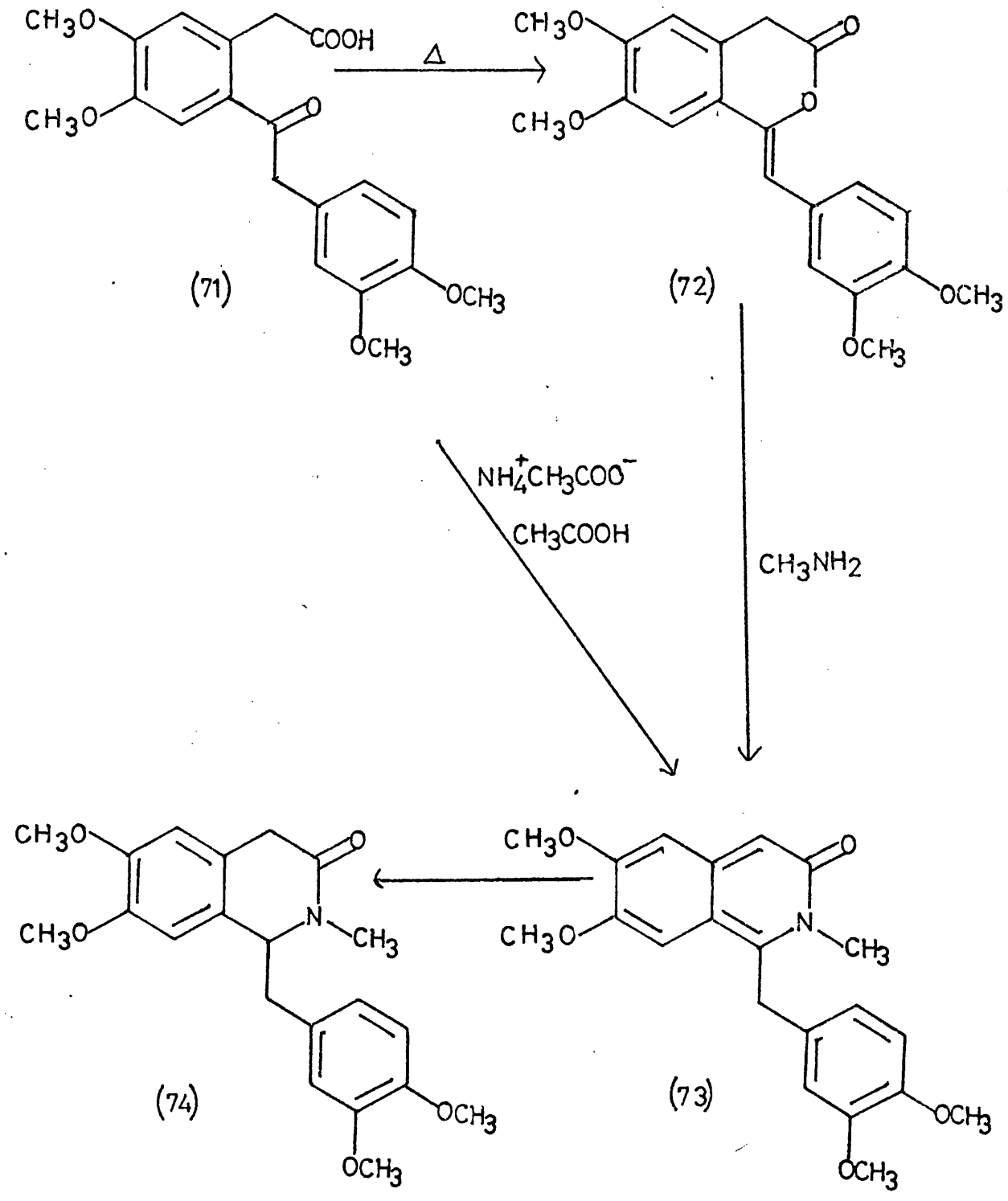
(67) (66)



(68)



(69) (70)


CH3O
CH3O
COOH
Δ
O
(71)
OCH3
OCH3
CH3O
CH3O
O
O
(72)
OCH3
OCH3
NH4+CH3COO−
CH3COOH
CH3NH2
CH3O
CH3O
O
N
CH3
(74)
OCH3
OCH3
CH3O
CH3O
O
N
CH3
(73)
OCH3
OCH3

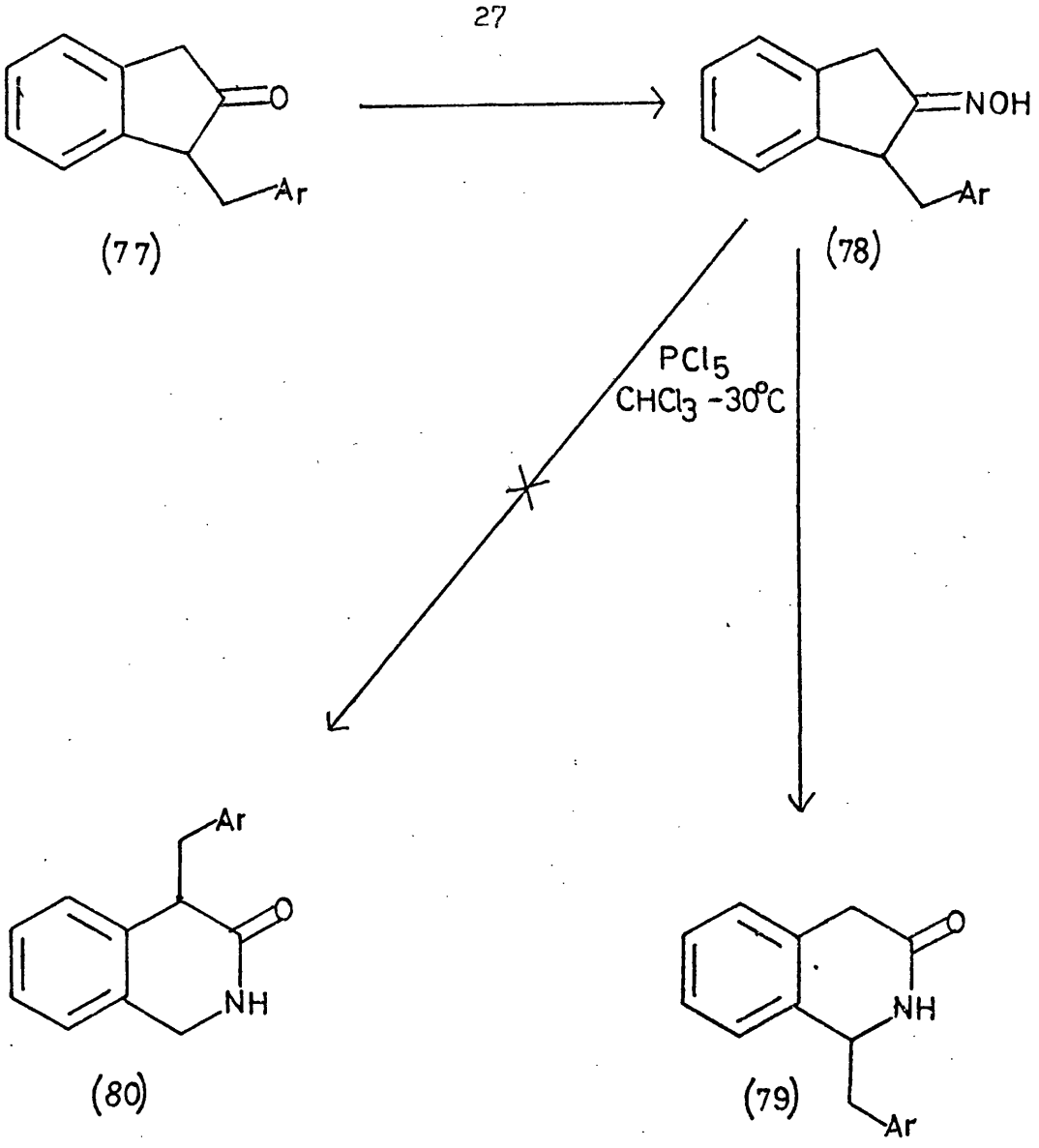
Syntheses involving ring expansions.

There have been several reports of syntheses of 1,4-dihydro-3(2H)-isoquinolinones which rely on the conversion of a 5-membered ring into a 6-membered ring by the insertion of a nitrogen atom. The most general appears to be a method reported by Lyle[42] in which the oxime(75) is subjected to a Beckman rearrangement thereby yielding the product(76).

(75) (76)

This method was improved and generalised by Jenson[43] who treated ketones(77) with hydroxylamine hydrochloride to form the corresponding oximes(78) which then yield the 1-substituted product (79). The alternative 4-substituted products(80) are not formed.

The ketone from which compound (75) was derived may also be converted into (76) by treatment with sodium azide followed by sulphuric acid[44].



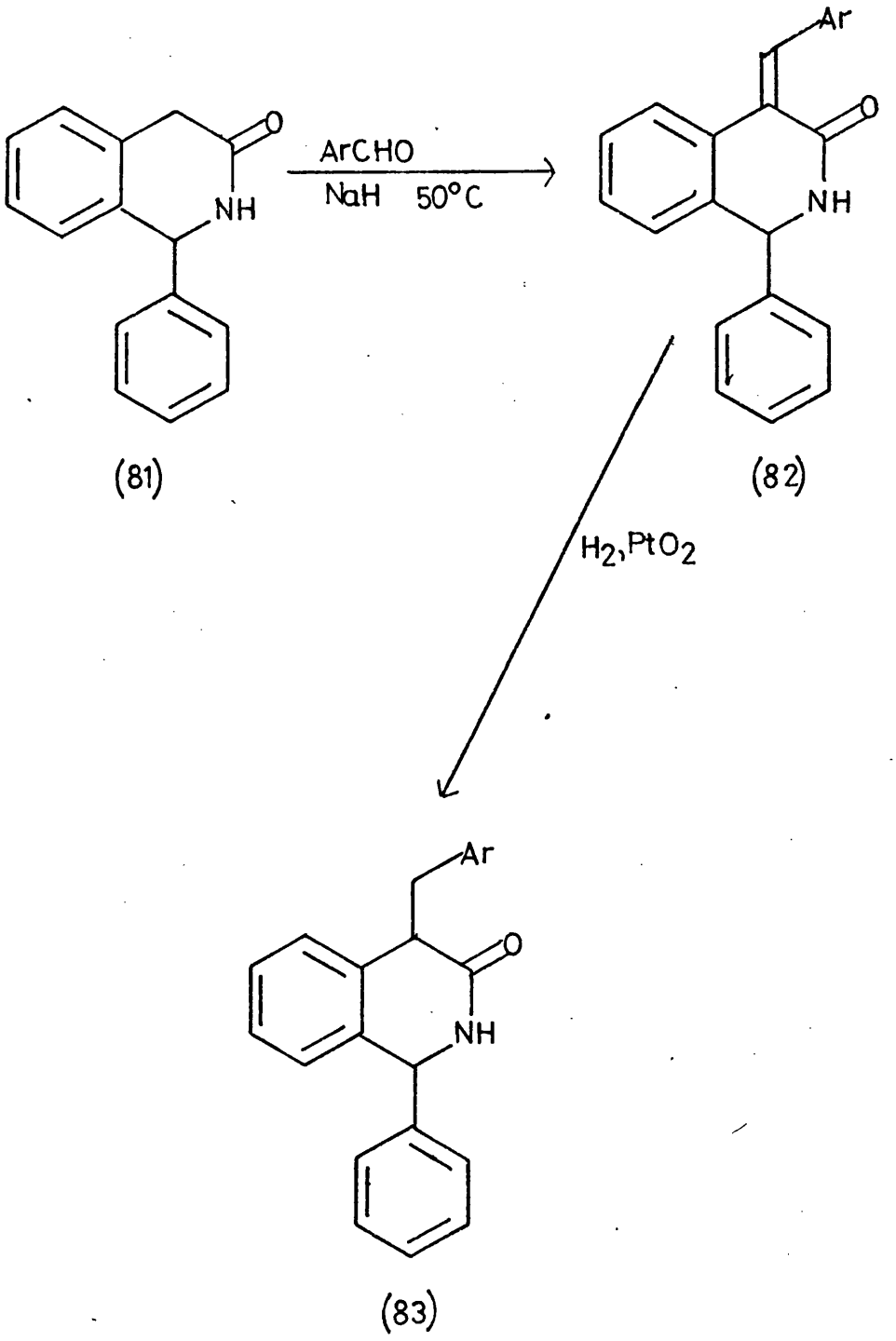
The incorporation of substituents after the formation of the isoquinolinone system.

The only position of substitution which will be considered is the 4-position as it is directly relevant to the research to be presented in this thesis.

Deak[45] has developed a method, which he later extended[46] involving the reaction of an isoquinolinone(81) with an aromatic aldehyde in the presence of sodium hydride to form the 4-benzylidene substituted isoquinolinone(82) which was

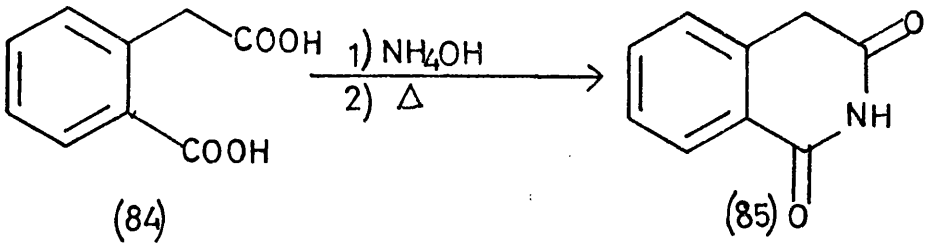
then catalytically reduced to give the 4-benzyl derivative(83). The reaction works well but so far only a small number of aldehydes have been tried.

Deak has also investigated the stereochemistry of the benzylidene compound(82)[47].



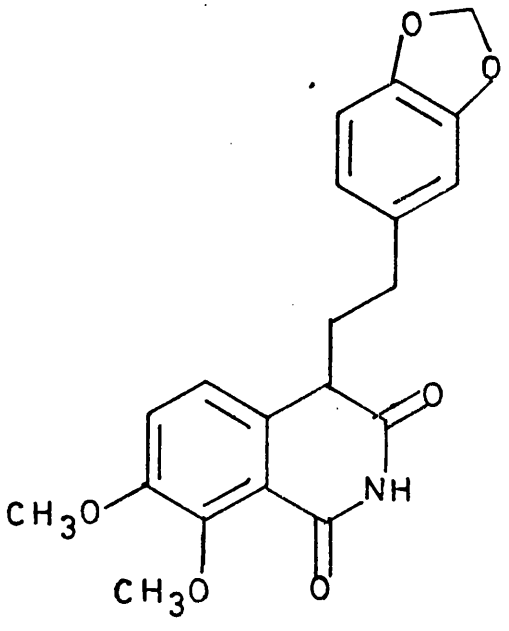
The Synthesis of 1,3-Isoquinolinediones

In contrast to the case of the 1,4-dihydro-3(2H)-isoquinolinones nearly all the reported syntheses of 1,3-isoquinolinediones use the method of Gabriel[48] in which a homophthalic acid derivative(84) is treated with ammonia to form the ammonium salt which is then heated to form the dione(85).



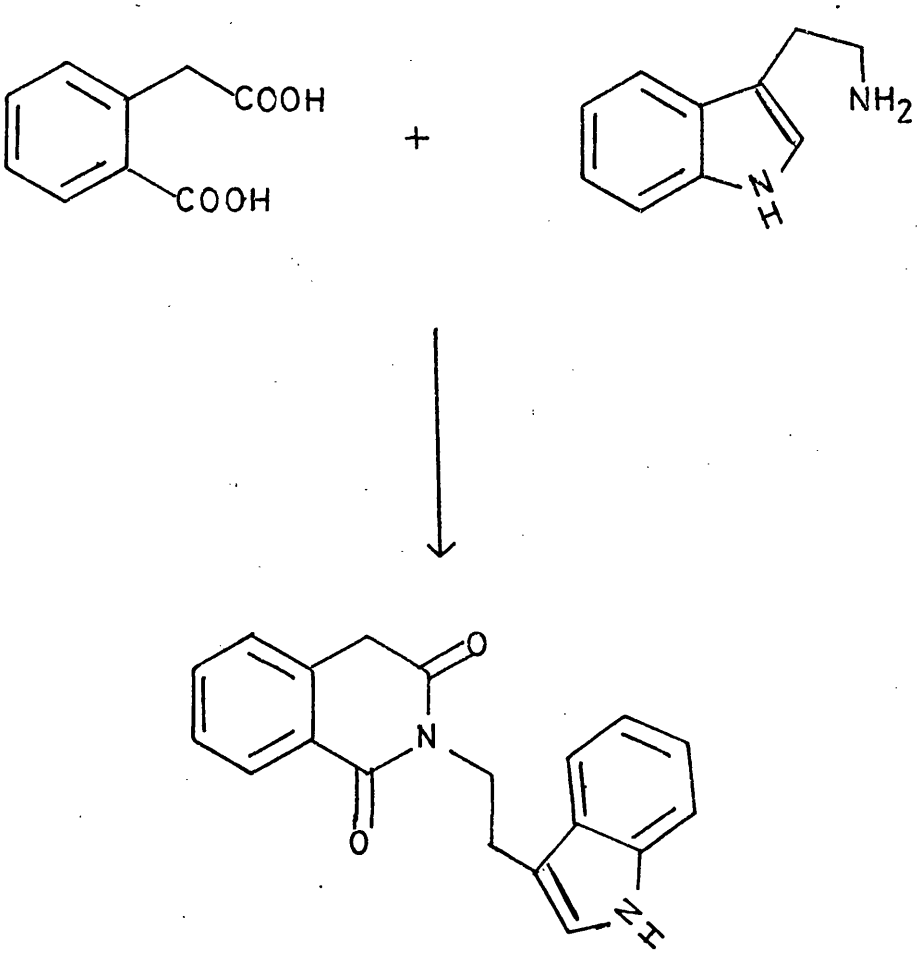
(84) (85)

Robinson for example used this method extensively as in the case of the isoquinoliedione(86)[49]. See also references 50, 51,52,53,54, for other examples.



(86)

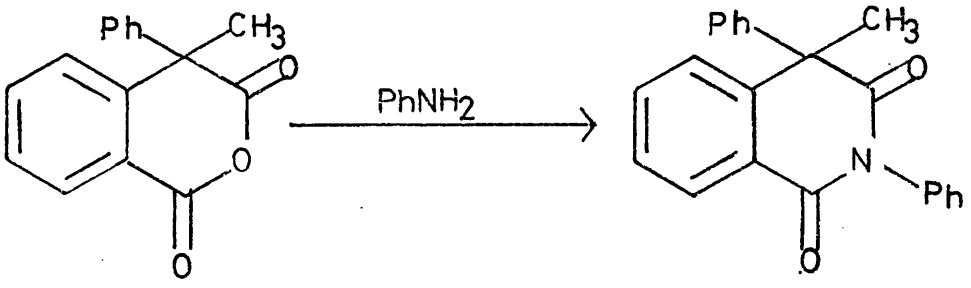
If a 2-substituted product is required then a primary amine is used in the place of ammonia, as for example the reaction between homophthalic acid and tryptamine to form the isoquinolinedione(87)[55].



(87)

See also references 56, 57, 58, 59, for other examples.

The homophthalic anhydride may be used in place of the acid, as in a synthesis by Anderson[60] in which the anhydride (88) is treated with aniline to produce the isoquinolinedione (89).



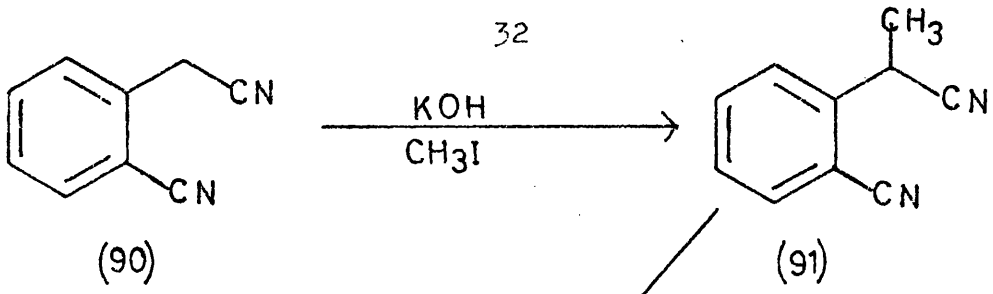
(88) (89)

See also references 61, 62, for other examples.

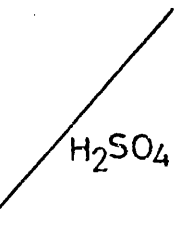
Other methods have been reported however, and some of these are included below.

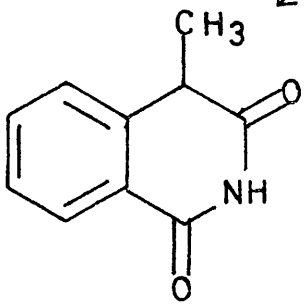
Gabriel[63] described a second synthesis which is a varient on the homophthalic acid route outlined above. In this case the dinitrile(91) was treated with sulphuric acid to form the isoquinolinedione(92). Interestingly a substituent group was introduced at the 4-position in this sequence through the action of potassium hydroxide and methyl iodide upon the dinitrile(90).

Hishimoto[64], applied a Curtius reaction to the carboxyisocarbostyrile(93) and was able to produce 1,3-isoquinolinedione(95) via the urethane(94).

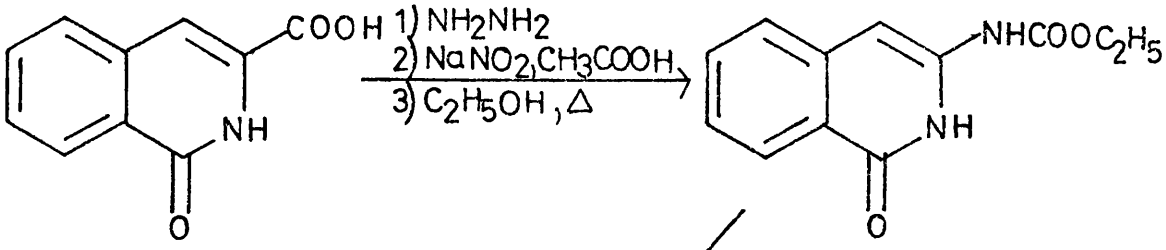


(90) (91)

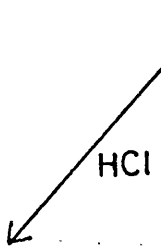


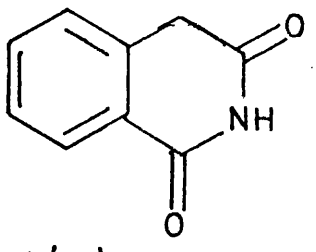


(92)



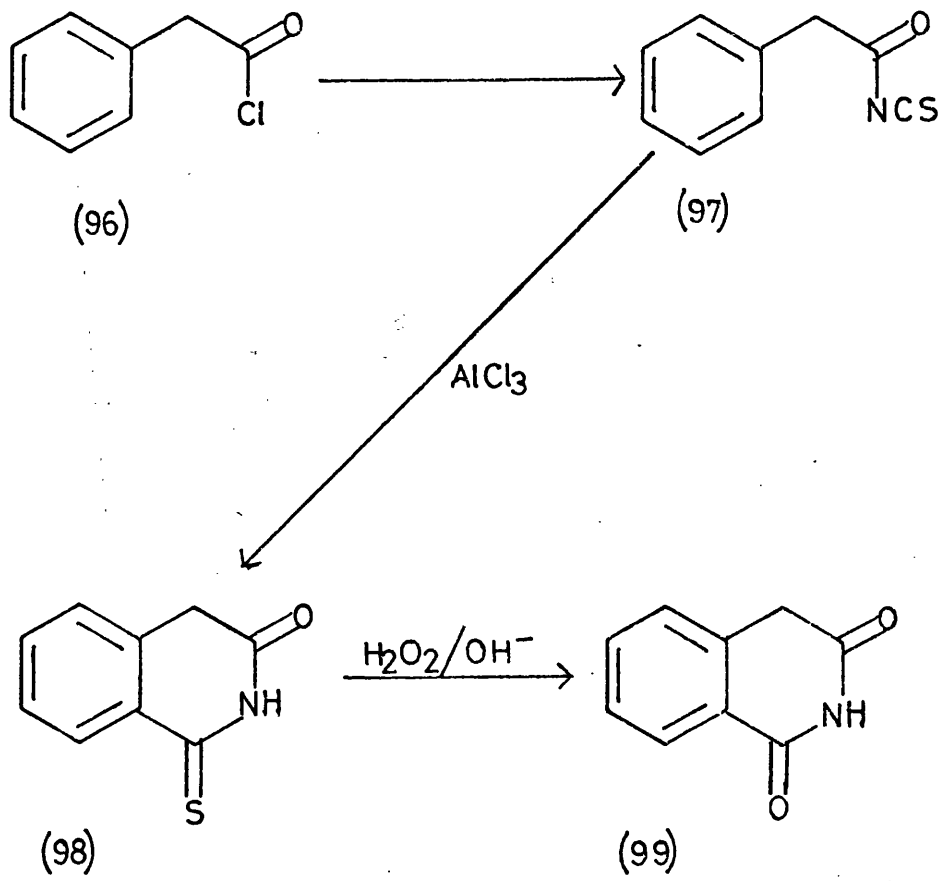
(93) (94)



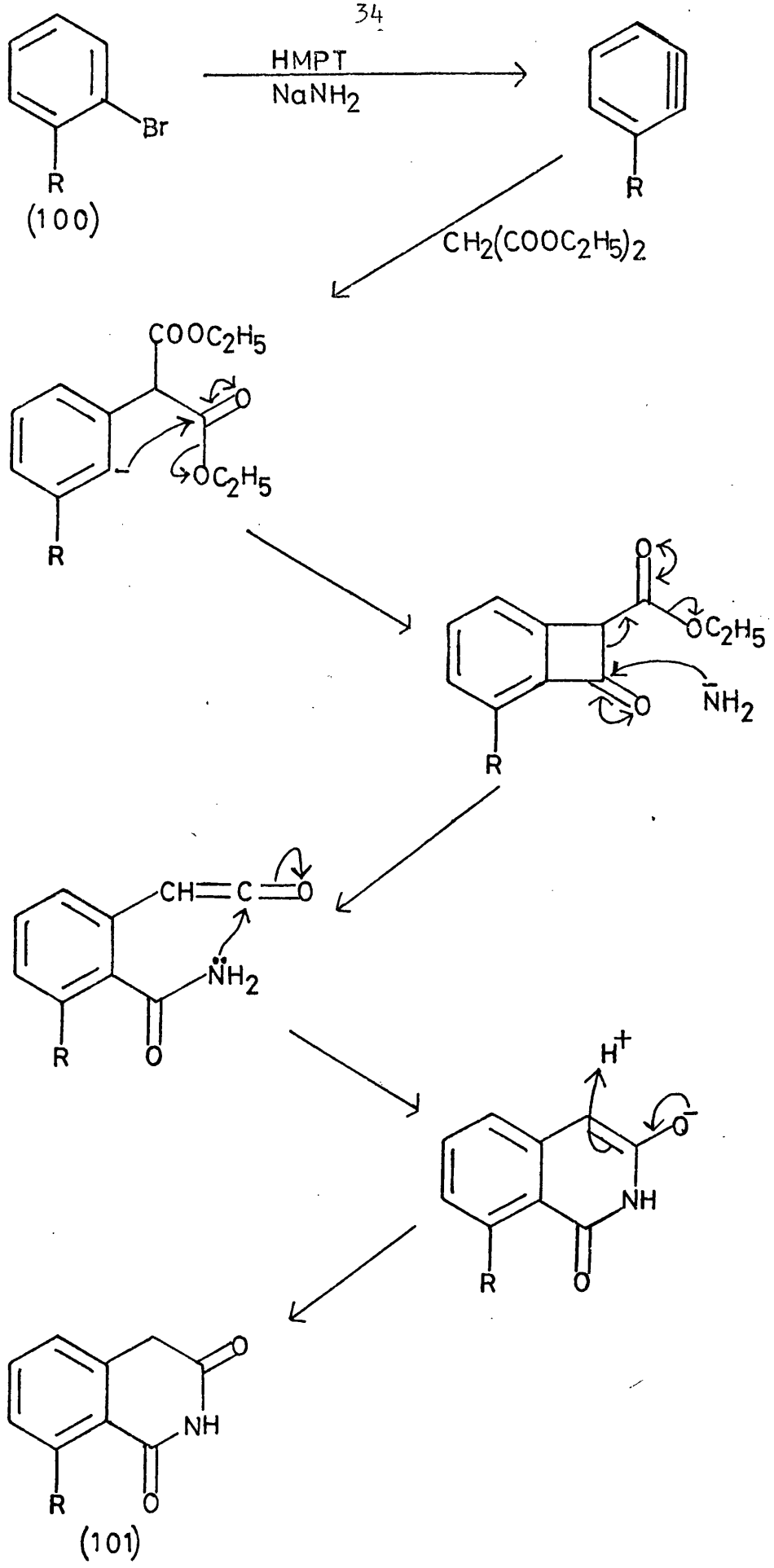


(95)

Another reaction sequence which is reported by Smith[65] may be of general applicability. Phenylacetyl chloride(96) was treated with lead thiocyanate to form the isothiocyanate(97) which, after ring closure to form the 1-thione(98), was oxidised using hydrogen peroxide to the 1,3-isoquinolinedione (99).

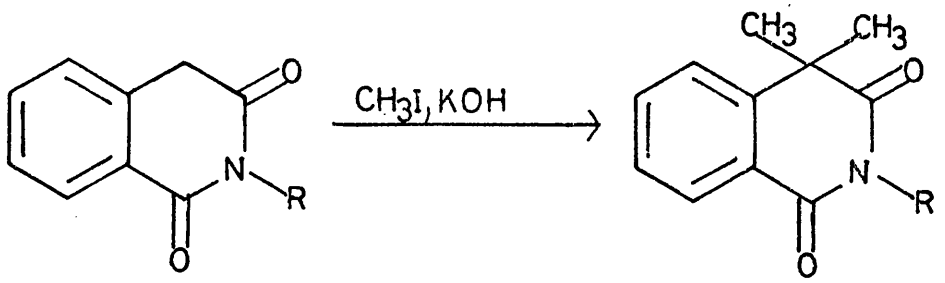


More recently Guyot[66] has developed a synthetic method involving an aryne intermediate to produce 8-substituted-1,3-isoquinolinediones. A 2-substituted bromobenzene(100) is treated with diethyl malonate in the presence of hexamethylphosphoramide and sodium amide to produce the product(101). A mechanism involving the intermediacy of a cyclobutane derivative proposed by the authors is shown.


HMPT
NaNH2
Br
R
(100)
CH2(COOC2H5)2
COOC2H5
OC2H5
NH2
CH=C=O
NH2
H+
NH
(101)

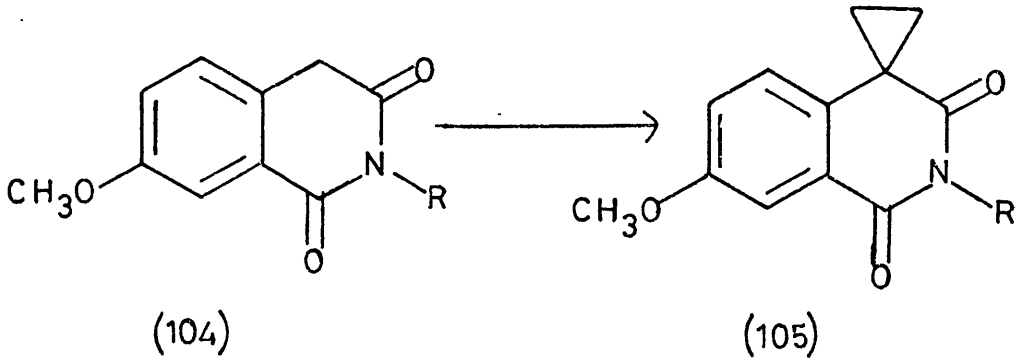
Incorporation of substituents after the formation of the 1,3-isoquinolinedione system.

Only 4-substitution will be discussed. Gabriel[67,68] treated both 1,3-isoquinolinedione and its 2-methyl analogue (102) with methyl iodide and potassium hydroxide to form the 4,4-dimethyl derivatives(103).



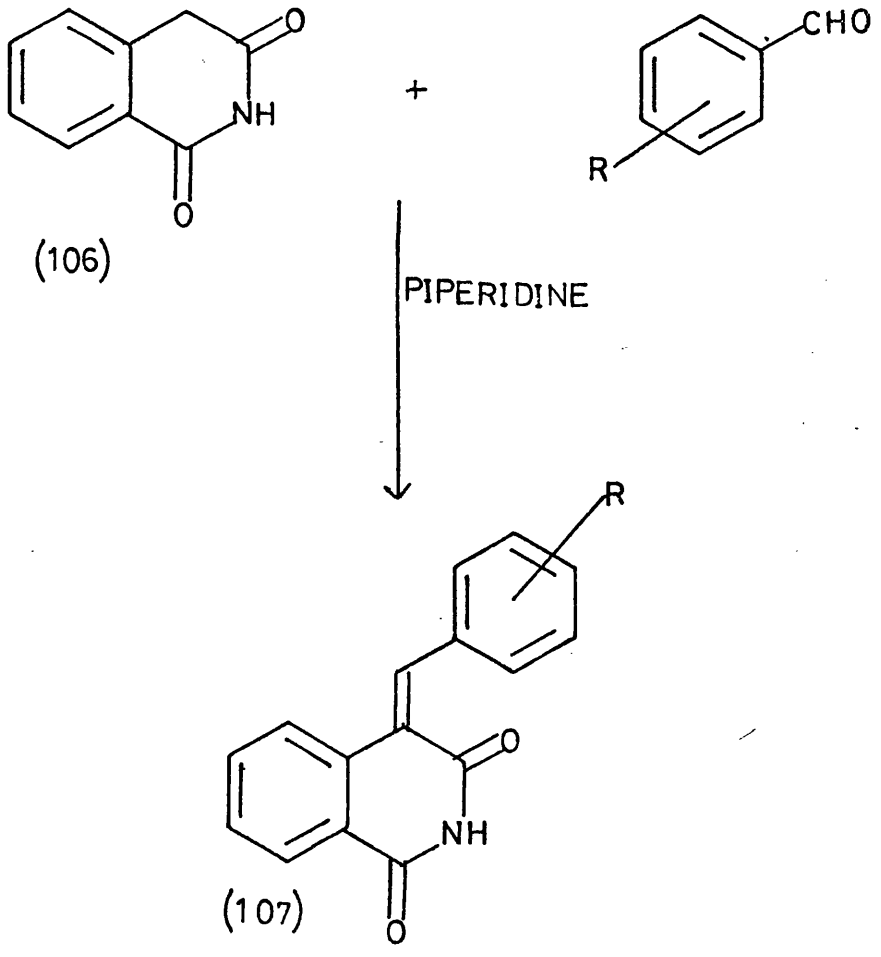
(102) (103)

Alkylations have also been performed using sodium ethoxide as the base[69,70] and the 4-acyl derivatives have been made by using potassium hydroxide and the appropriate acyl chloride[71]. Recently[72,73] spiro compounds have been formed using similar techniques. The isoquinolinedione(104) for instance when treated with 1-chloro-2-bromoethane in the presence of sodium hydride was converted into the spiro compound(105)[73]. The structure of this compound was comfirmed by the opening of the cyclopropane ring with a secondary amine.



(104) (105)

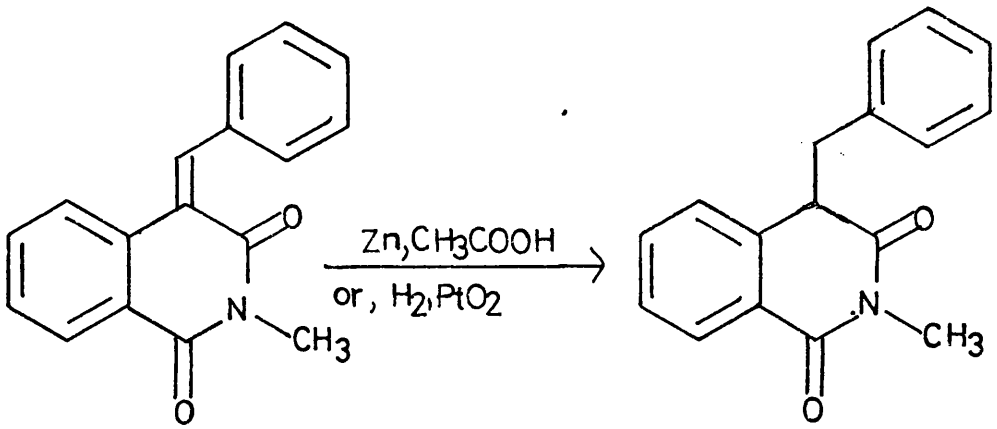
4-Benzylidene derivatives(107) can be prepared by the condensation of a 1,3-isoquinolinedione(106) with an aromatic aldehyde in the presence of piperidine[74].



(106) (107)

This method was later extended by Meyer[75] to include several more aromatic aldehydes although methoxy-substituted benzaldehydes were not tried. The condensation was also investigated by Dabard[76] who examined the reaction of a variety of substituted benzaldehydes with various 2-substituted 1,3-isoquinolinediones.

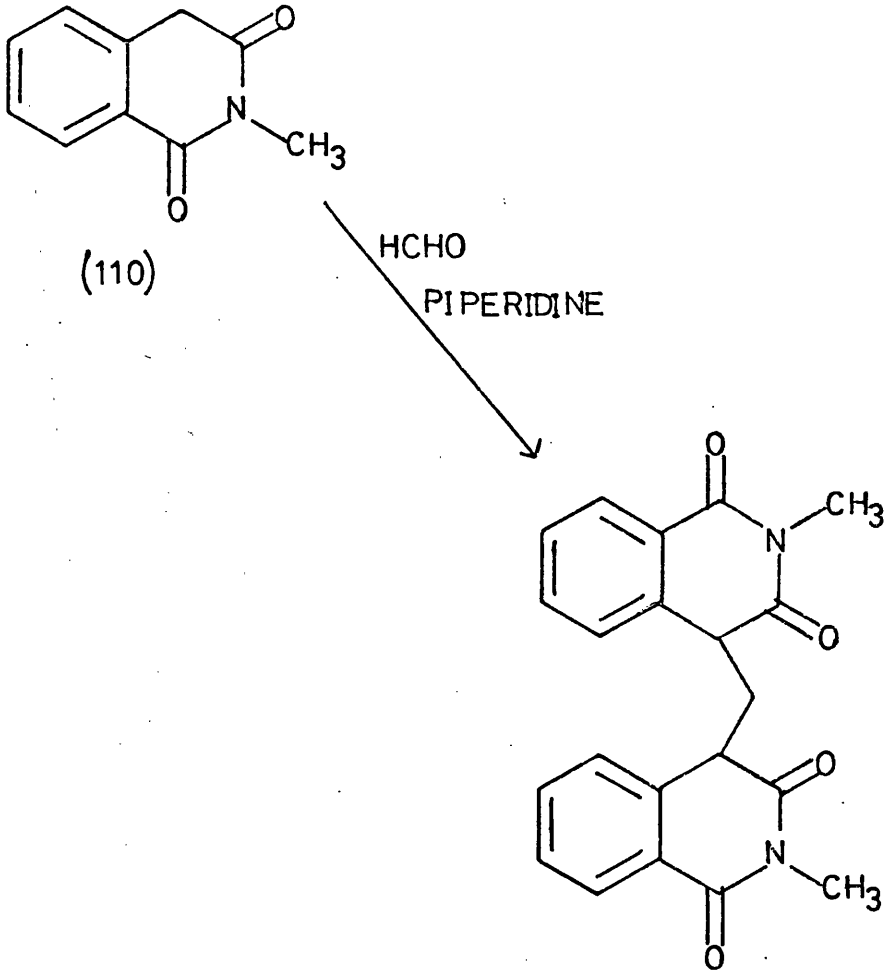
The reaction is also successful using pyridine as the catalyst[77]. 4-Benzylidene-substituted 1,3-isoquinolinediones may be reduced to the corresponding 4-benzyl derivatives by either zinc and acetic acid[78,79] or catalytic hydrogenation[80] as in the case of the isoquinolinedione(108) which may be reduced to the 4-benzyl derivative(109) by either catalytic hydogenation using Adams catalyst or zinc and acetic acid.



(108) (109)

Condensation of 1,3-isoquinolinediones with aliphatic alcohols leads to the formation of the intermediate alcohol and not the dehydrated product[81]. Anomalous results are

obtained in the case of formaldehyde which produces a variety of products depending upon the conditions employed. 2-Methyl-1,3-isoquinolinedione(110) reacts with formaldehyde at room temperature in the presence of piperidene to produce the bis-isoquinolinedione(111).



(110)

(111)

The Synthesis of 1,2,3,4-Tetrahydroisoquinolines.

1,2,3,4-Tetrahydroisoquinolines may be prepared by methods which may be classified as follows:-

1) Reduction of the following:-

a) isoquinolines.

b) 3,4-dihydroisoquinolines.

c) quaternary salts of isoquinolines.

d) quaternary salts of 3,4-dihydroisoquinolines.

e) isoquinolinones .

2) formation resulting directly from a cyclisation reaction

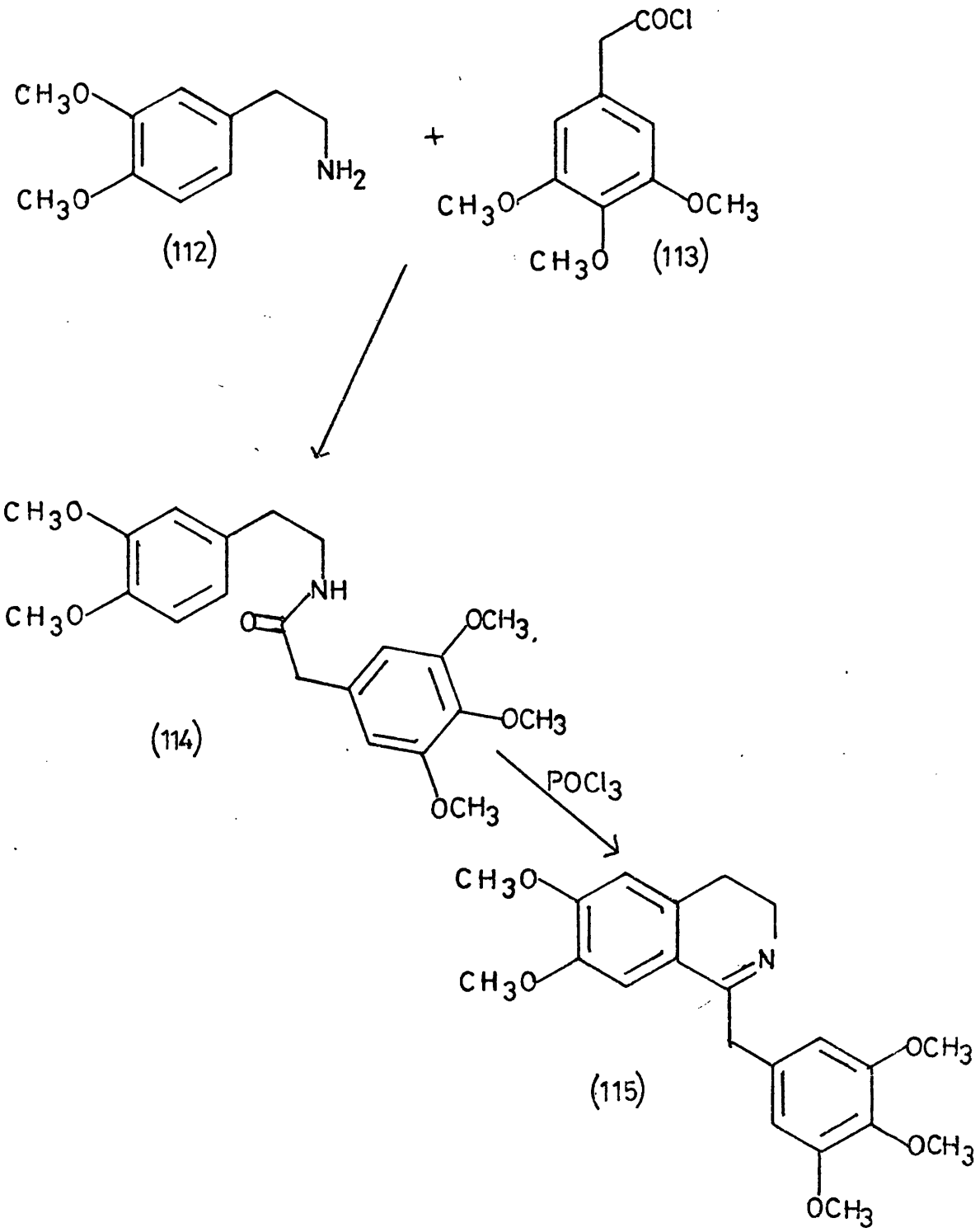
Methods of synthesizing isoquinolinones have already been discussed and before a discussion of the methods indicated above is commenced the available methods for the synthesis of isoquinolines and 3,4-dihydroisoquinolines will be outlined. The syntheses of both these types of compound have been extensively reviewed and it is not the author's intention to present such a review here. Instead the main methods of synthesis will be outlined and reference made to appropriate review articles.In addition some methods from the recent literature will be included.

The synthesis of isoquinolines and 3,4-dihydroisoquinolines.

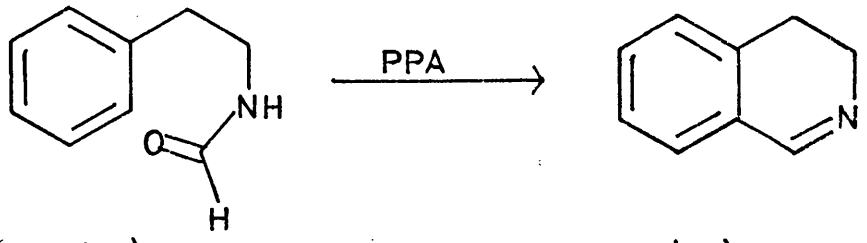
The Bichler-Napieralski reaction.

For reviews of th ring-closure reaction itself see references 82,83,84,85,86,87, and for guides to the preparation of the necessary substrates see references 88,85,89,90. The original method which yields a 3,4-dihydroisoquinoline as the initial product[91] depends upon the ring closure of a β-arylethylamide with a mixture of phosphoryl chloride and

phosphoric oxide. The product a 3,4-dihydroisoquinoline may then be oxidised to the fully aromatic isoquinoline or reduced to the 1,2,3,4-tetrahydroisoquinoline. For example the β-arylamine(112) when treated with the acid chloride(113) forms the β-arylamide(114) which on treatment with phosphoryl chloride yields the 3,4-dihydroisoquinoline(115)[92].



Many agents other than a phosphoryl chloride and phosphoric acid mixture have been used, for example phosphoryl chloride[93,94], and phosphoric oxide in pyridine[95]. More recently polyphosphoric acid has been recommended and is especially useful for the cyclisation of formamides[96] as in the case of the amide(116) which was cyclised to give 3,4-dihydroisoquinoline(117).

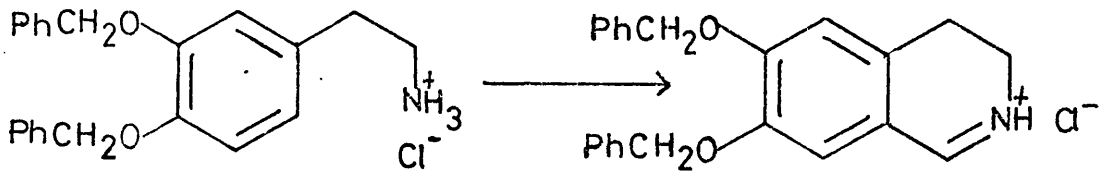


(116) (117)

Polyphosphoric ester (PPE) is another relatively modern reagent and requires less severe conditions than many of the older cyclisation agents.

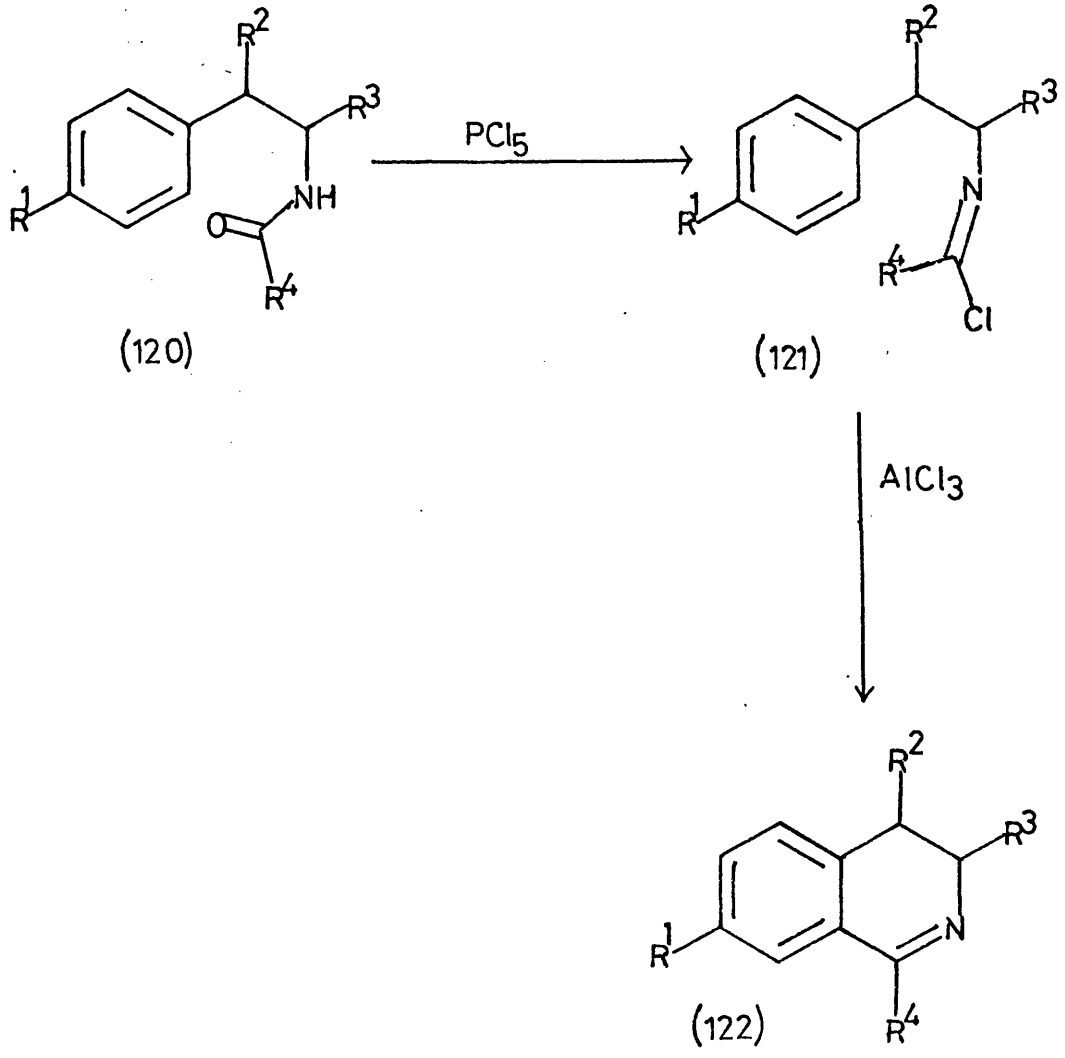
Modifications of the Bichler-Napieralski reaction.

A useful modification of the reation which was reported by Kador[97] is especially useful for the preparation of 1-unsubstituted isoquinolines. The hydrochloride salt of the amine (118) is treated with trichloroacetaldehyde and phosphoryl chloride to form the 3,4-dihydroisoquinolinium salt(119).



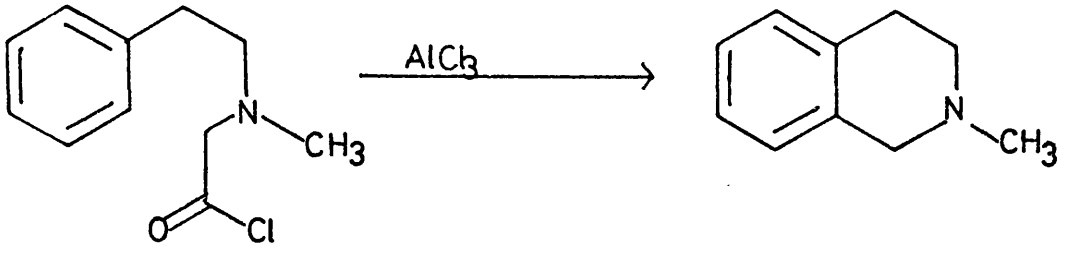
(118) (119)

Hey[98] reported a method whereby, if a normal Bichler-Napieralski reaction fails, the amide(120) can be converted with phosphorous pentachloride to an imidoyl chloride(121), which is then cyclised using aluminium chloride to the dihydroisoquinoline(122).



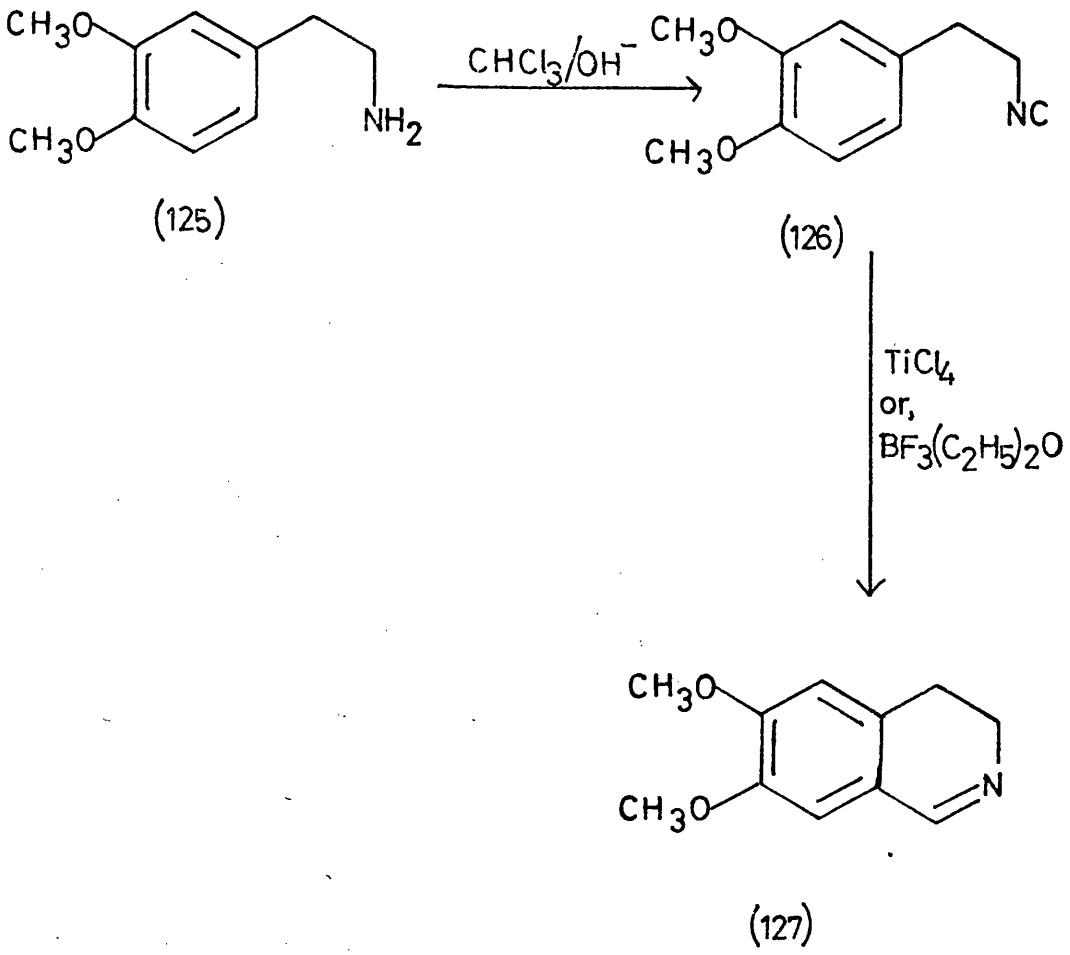
(120) (121) (122)

Aluminium chloride or phosphoric oxide have also been used to convert methyl-β-phenylethylaminoacetyl chloride(123) into the tetrahydroisoquinoline(124)[99,100], but this approach is limited to those substrates that are free from alkoxy substituents.



(123) (124)

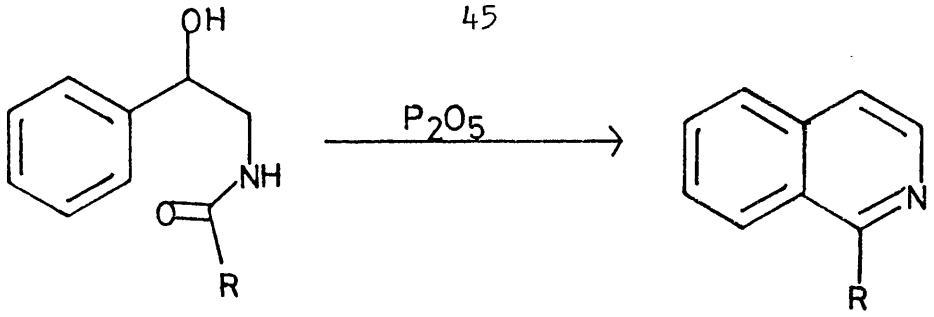
Ban has reported an interesting modification of the Bichler-Napieralski reaction[101], in which the amine(125) is treated with dichlorocarbene to form the isocyanide(126) which is then cyclised using either titanium tetrachloride or borontrifluoride etherate to the dihydroisoquinoline(127).



(125) (126) (127)

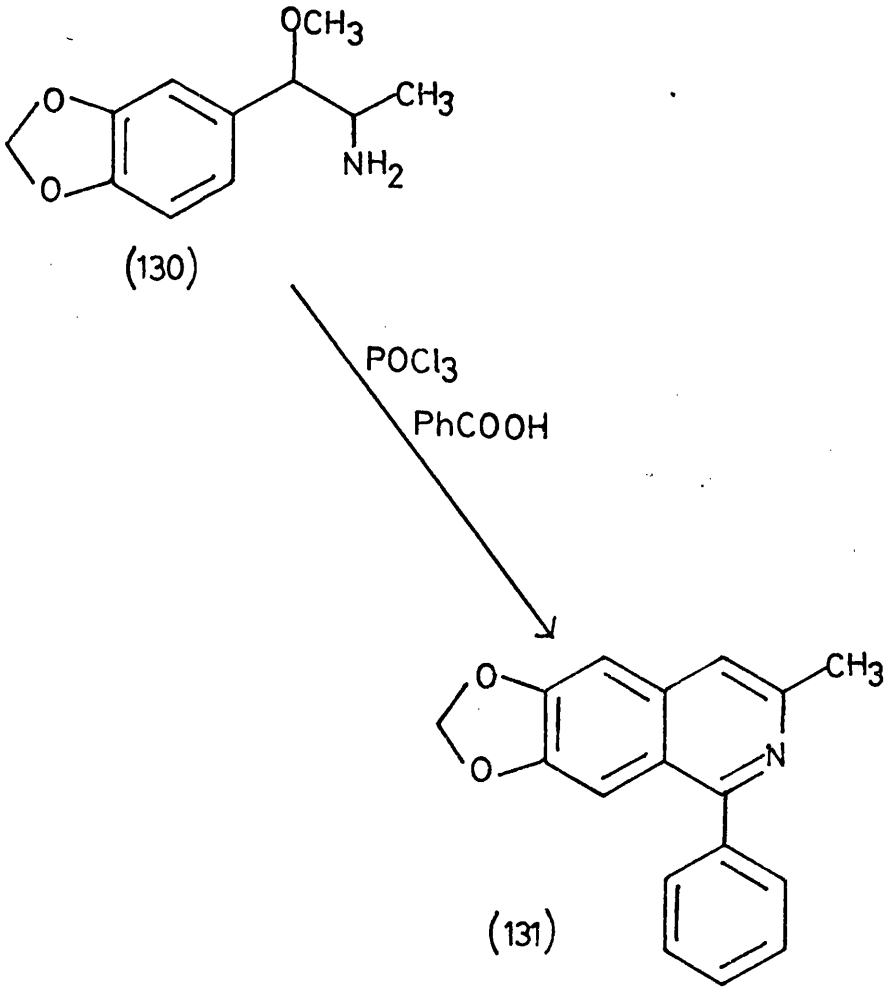
The Pictet-Gams reaction[84]

This is a modification of the Bichler-Napieralski reaction which leads directly to the formation of the fully aromatic isoquioline(129) by starting with a β-hydroxy or β-methoxy substituted amide(128). Syntheses of the appropriate amides (128)have been reviewed[102,103,104].



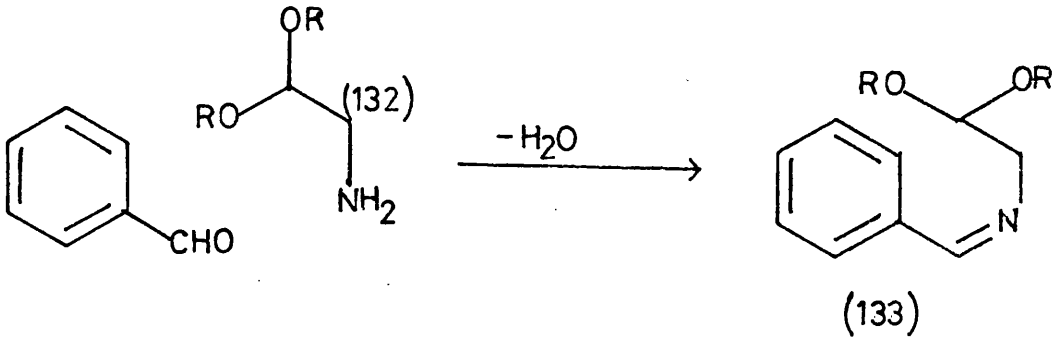
(128) (129)

Isolation of the β-arylethylamide is not always necessary as is demonstrated in the case of the amine(130) which is converted directly into the isoquinoline(131)[105] by heating with a mixture of benzoic acid and phosphoryl chloride.

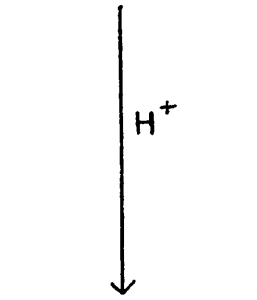


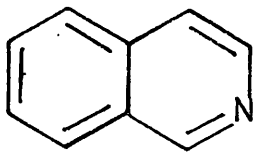
The Pomeranz-Fritsch reaction[50,83,24,87].

In this reaction ring closure occurs between the aryl ring and what will become the 4-position in the final isoquinoline. A benzaldehyde is first condensed with an aminoacetaldehyde dialkylacetal(132) to form the Schiff's base(134) which is cyclised with sulphuric acid to the isoquinoline(135).



(133)

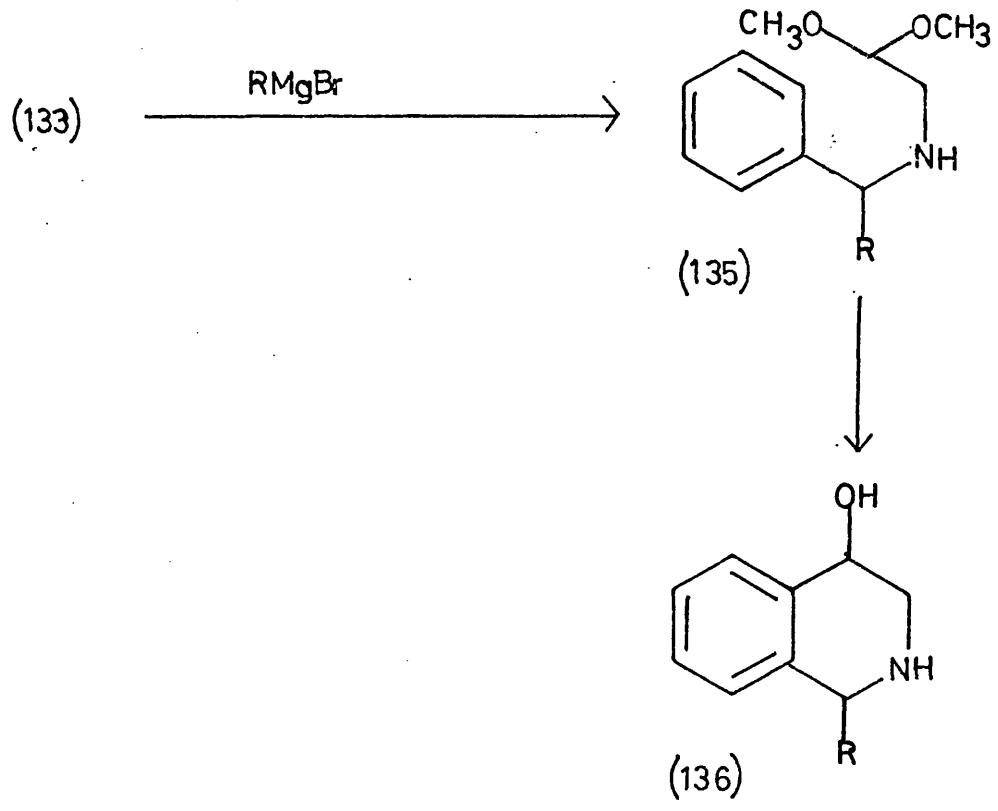




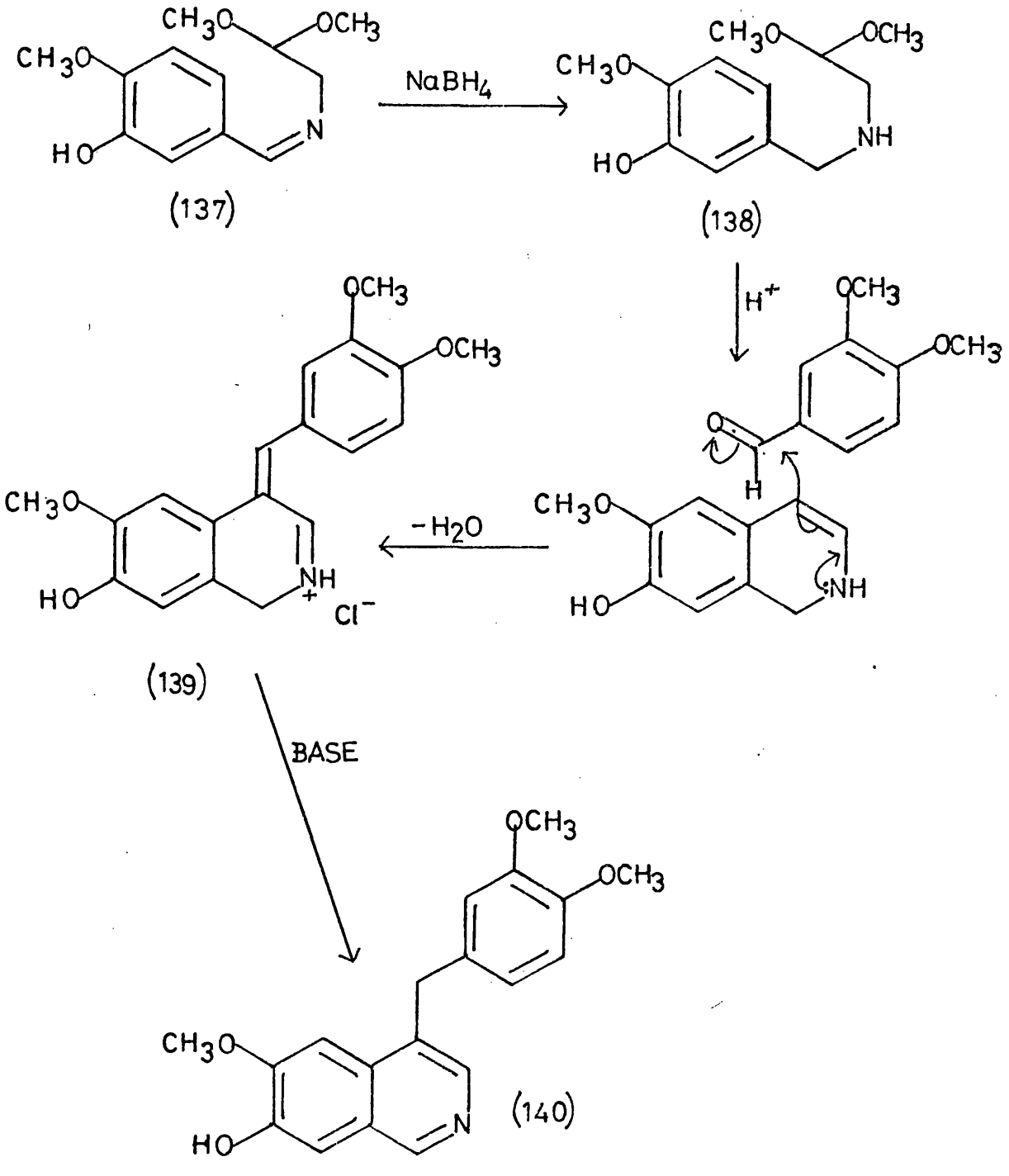
(134)

Bobbitt[106,107] has modified the reaction by catalytically reducing the corresponding amine, which is then treated with 6M hydrochloric acid and either a 4-hydroxy-1,2,3,4-tetrahydroisoquinoline[108] or a 1,2-dihydroisoquinoline[109] is formed depending upon the conditions employed. If the resultant acidic solution is hydrogenated the corresponding 1,2,3,4-tetrahydroisoquinoline is formed. The fully aromatic isoquinoline is best prepared by treating the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline with N-bromosuccinimide followed by acid catalysed dehydration of the intermediate 4-hydroxy-3,4-dihydroisoquinoline.

1-Substituted isoquinolines may be prepared by a similar route whereby the Schiff's base(133) is treated with one equivalent of a Grignard reagent to form the amine(135) which may then be cyclised to the 1-substituted isoquinoline(136).

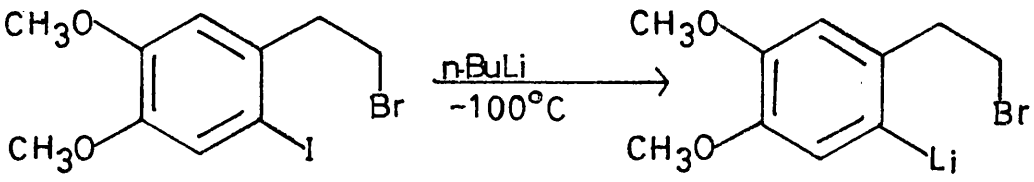


Bobbitt further extended the reaction[110] to incorporate a 4-benzyl substituent by treating the amine(138), prepared from the Schiff's base(137), with a benzaldehyde followed by 6M hydrochloric acid. The resulting benzylidene substituted 1,4-dihydroisoquinolinium salt(139) was then treated with a base to form the isoquinoline(140)[111].

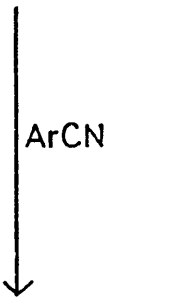


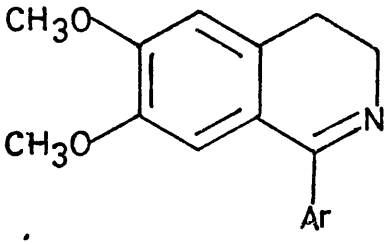
Other methods.

3,4-Dihydroisoquinolines have been synthesised by treating an aryl lithium compound such as (141) with an aryl cyanide to produce the 1-aryl substituted product (142)[112, 113].



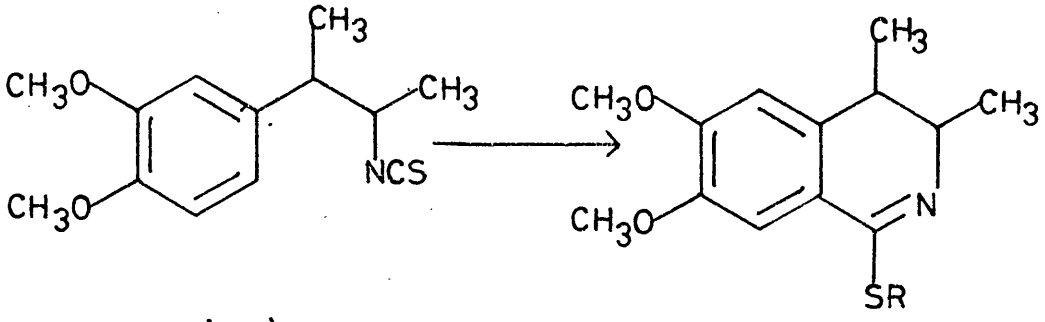
(141)





(142)

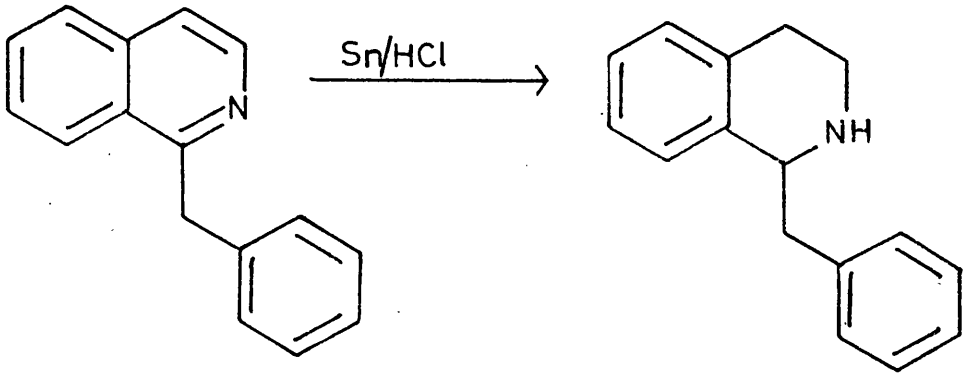
1-Alkylthio-3,4-dihydroisoquinolines have been synthesised in good yields by treating the appropriate thiocyanate(143) with a trialkyloxonium tetrafluoroborate to form the 1-alkylthio derivative(144)[114]. Various substituents at the 3,4,6 and 7 positions were possible.



(143) (144)

Reduction of isoquinolines and isoquinoline derivatives.

Isoquinolines. Isoquinolines may be reduced chemically to 1,2,3,4-tetrahydroisoquinolines by the use of tin and hydrochloric acid. e.g. reduction of (145) to (146)[115].



(145) (146)

Sodium in liquid ammonia has also been used for this type of reduction[116] and more rarely sodium borohydride[117] or lithium aluminium hydride[118] have been used. In addition isoquinoline itself has been reduced to 1,2,3,4-tetrahydroisoquinoline by the use of sodium in ethanol[119].

Isoquinolines may also be reduced catalytically using platinium dioxide to produce the 1,2,3,4-tetrahydroisoquinoline in neutral solution, but under acidic conditions the decahydroisoquinoline may be formed[120,121].

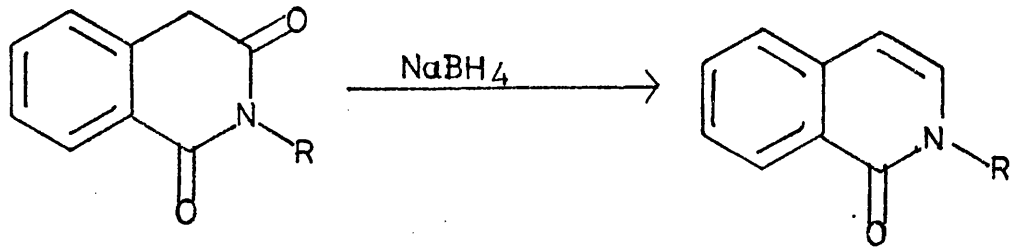
Raney nickel[122] and copper chromite[123,124] have also been used successfully as catalysts although very few examples have been reported.

3,4-Dihydroisoquinolines. 3,4-Dihydroisoquinolines may be reduced to 1,2,3,4-tetrahydroisoquinolines by either sodium borohydride[125] or catalytic reduction using either platinum dioxide[126,127,128], palladium[129,128] or nickel[122] catalysts.

Isoquinolium salts. Isoquinolinium salts are reduced to either 1,2,3,4-tetrahydroisoquinolines or 1,2-dihydroisoquinolines with sodium borohydride[130,131] or to 1,2-dihydroisoquinolines with lithium aluminium hydride[118].

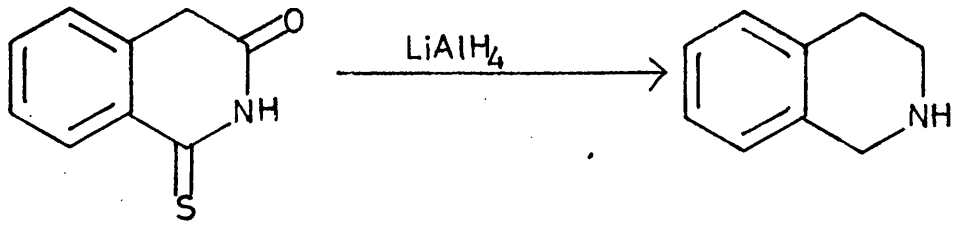
3,4-Dihydroisoquinolinium salts. 3,4-Dihydroisoquinolinium salts may be reduced to 1,2,3,4-tetrahydroisoquinolines using either lithium aluminium hydride or sodium borohydride[132,133]. Zinc and hydrochloric acid may also be used[134].

Isoquinolinones. 1,3-Isoquinolinediones(147) have been reduced to 1(2H)-isoquinolinones(148), using sodium borohydride[135]. 3,4-Dihydro-1(2H)-isoquinolinones may be reduced to tetrahydroisoquinolines using lithium aluminium hydride[136,137] or, more rarely, sodium borohydride[138].



(147) (148)

1,4-Dihydro-3(2H)-isoquinolinones[16] and 1,2-dihydro-4(3H)-isoquinolinones[139] can both be reduced to 1,2,3,4-tetrahydroisoquinolines using lithium aluminium hydride and the 1-thio-3(2H)-isoquinolinone (98) is also converted into 1,2,3,4-tetrahydroisoquinoline (150) with this reagent[140].

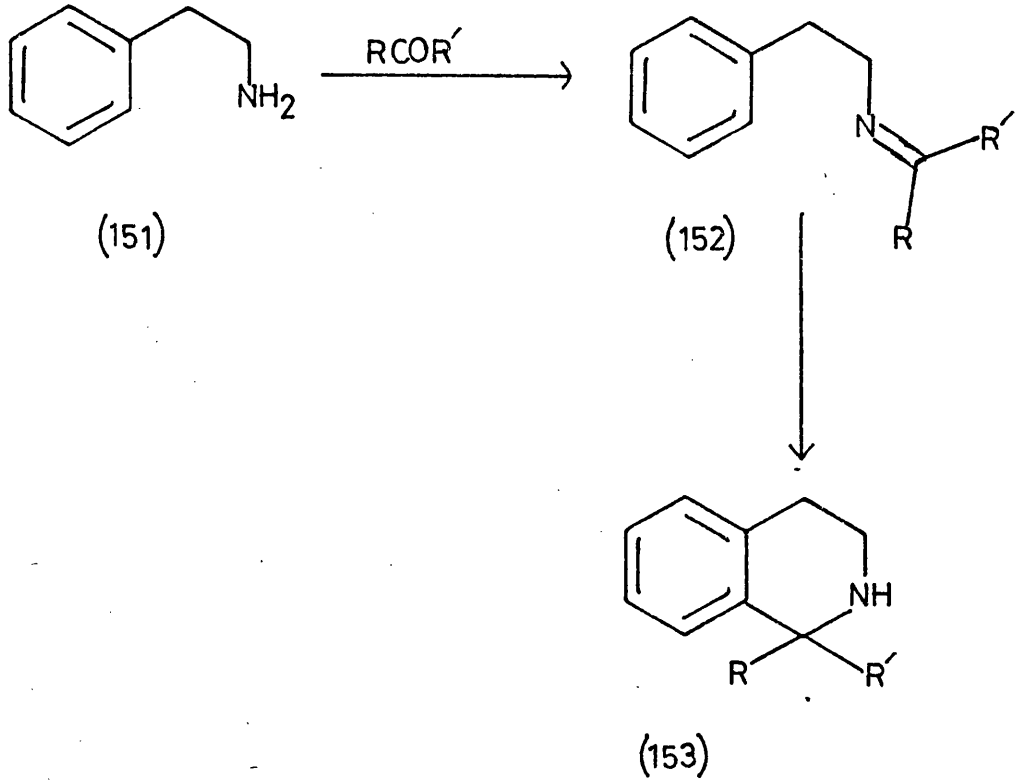


(149) (150)

"Direct"synthesis of 1,2,3,4-tetrahydroisoquinolines.

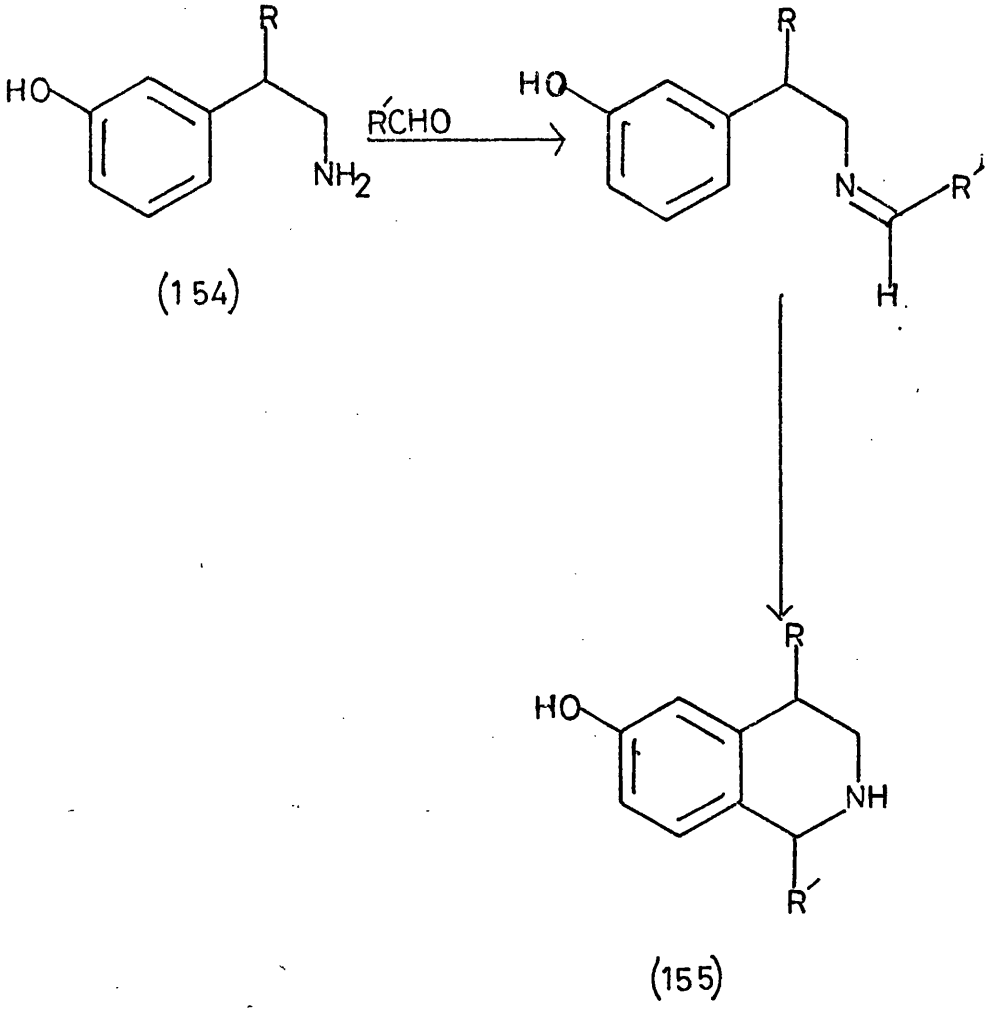
The Pictet-Spengler reaction[84] is the most common reaction of this type and may be regarded as a special case of the Mannich reaction. A β-arylethylamine(151) is first condensed with an aldehyde or ketone in the presence of concentrated

hydrochloric acid thus forming the imine(152). Ring closure then gives the tetrahydroisoquinoline(153) directly.



(151) (152) (153)

Kametani has stated that the external acid catalyst is not necessary if a phenolic group is present in the aryl ring in a position para to the point of ring closure[141] as in the sequence (154)-(155).

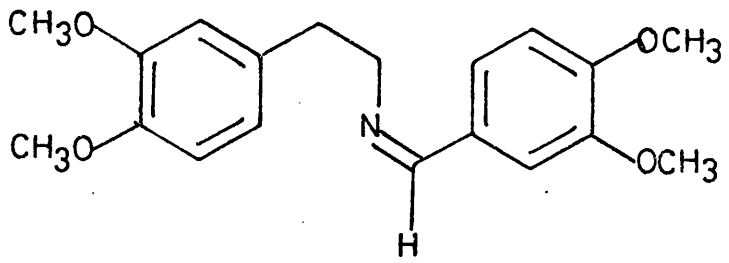


(154)

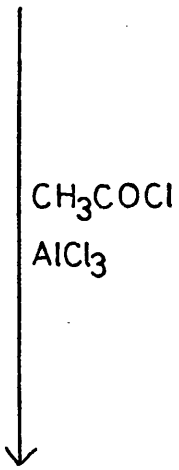
(155)

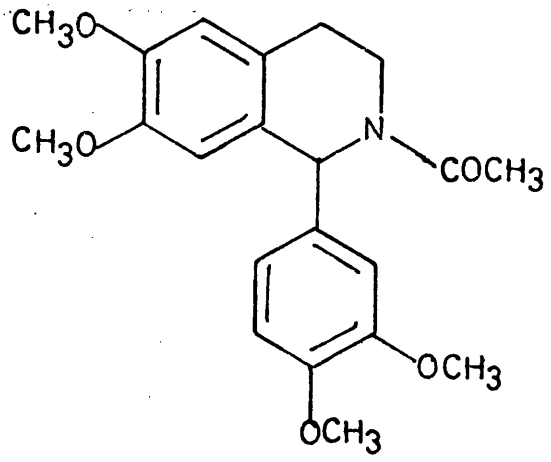
A methoxy group has been shown to have a similar effect[142].

Mollov[143] has reported a related reaction in which a 1,2,3,4-tetrahydroisoquinoline is formed. For example, the imine (156) reacts with acetyl chloride in the presence of aluminium chloride to form the tetrahydroisoquinoline(157).


CH3O
CH3O
N
H
OCH3
OCH3

(156)


CH3COCl
AlCl3


CH3O
CH3O
N
COCH3
OCH3
OCH3

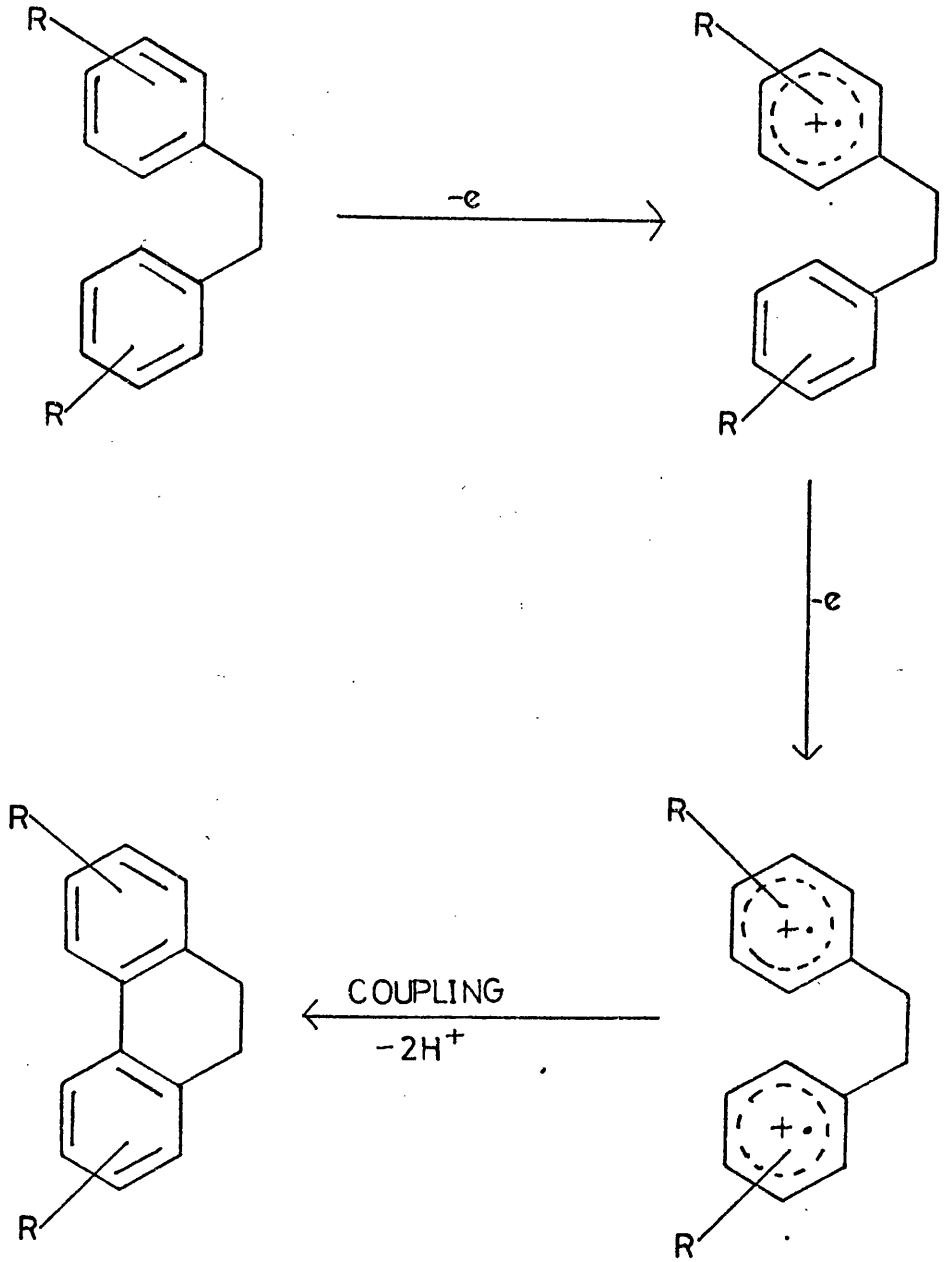
(157)

The Mechanism of Aryl-aryl Electrochemical Oxidative Coupling.

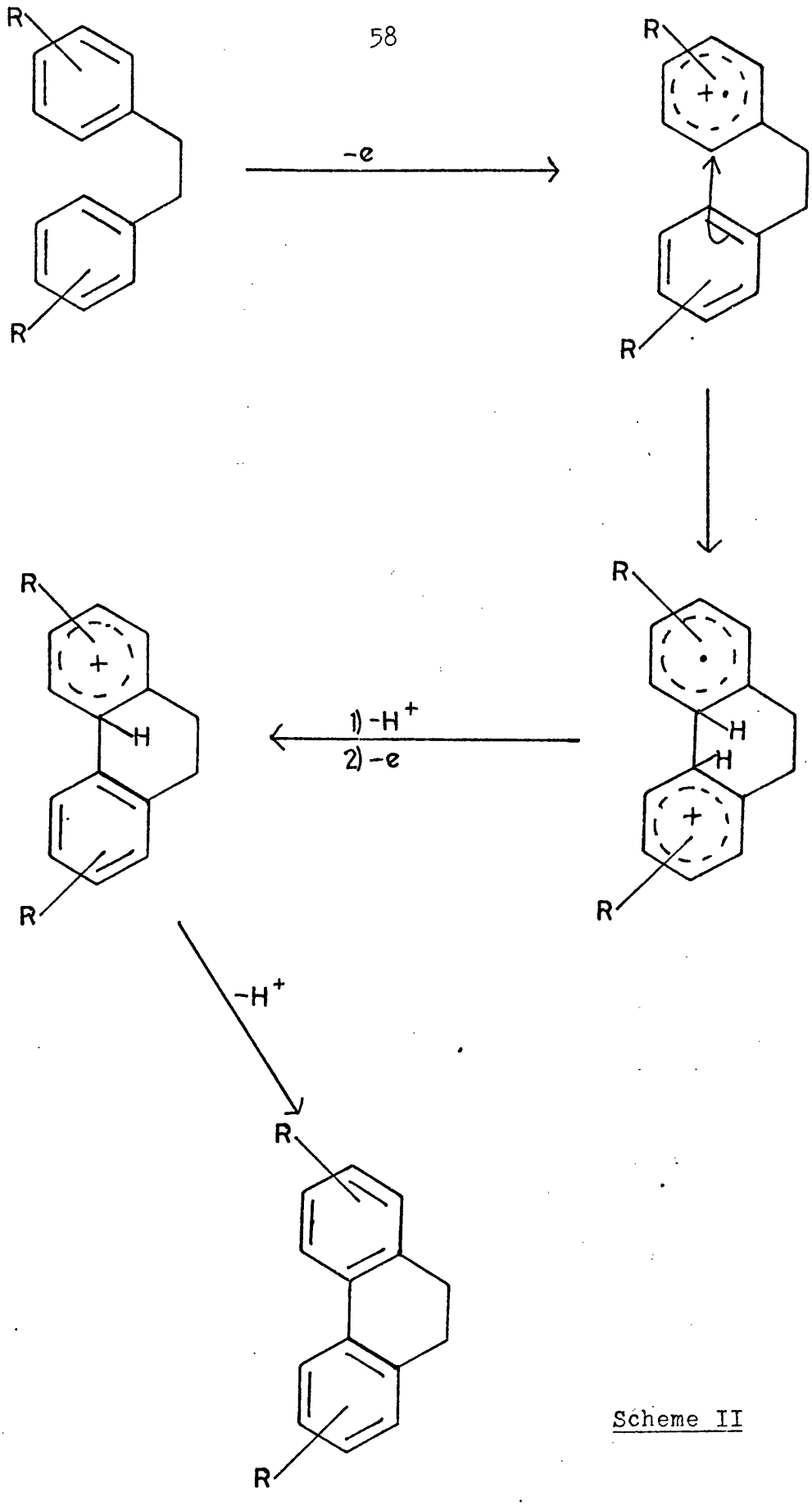
The precise mechanism by which two aryl rings couple electrochemically is not known but two principal mechanisms have been put forward. The first involves the simultaneous coupling of two radical cations followed by loss of two protons to form the coupled product (Scheme I)[144,145]. In the second mechanism a radical cation is attacked by a neutral aryl ring to form an intermediate radical cation which undergoes proton loss and further oxidation to yield the biaryl (Scheme II)[146].

On balance there is more evidence for the former mechanism but the latter cannot be ruled out. It is possible for instance that both mechanisms may operate simultaneously, the proportion of product formed *via* each route depending upon such factors as the nature of the aryl substituents.

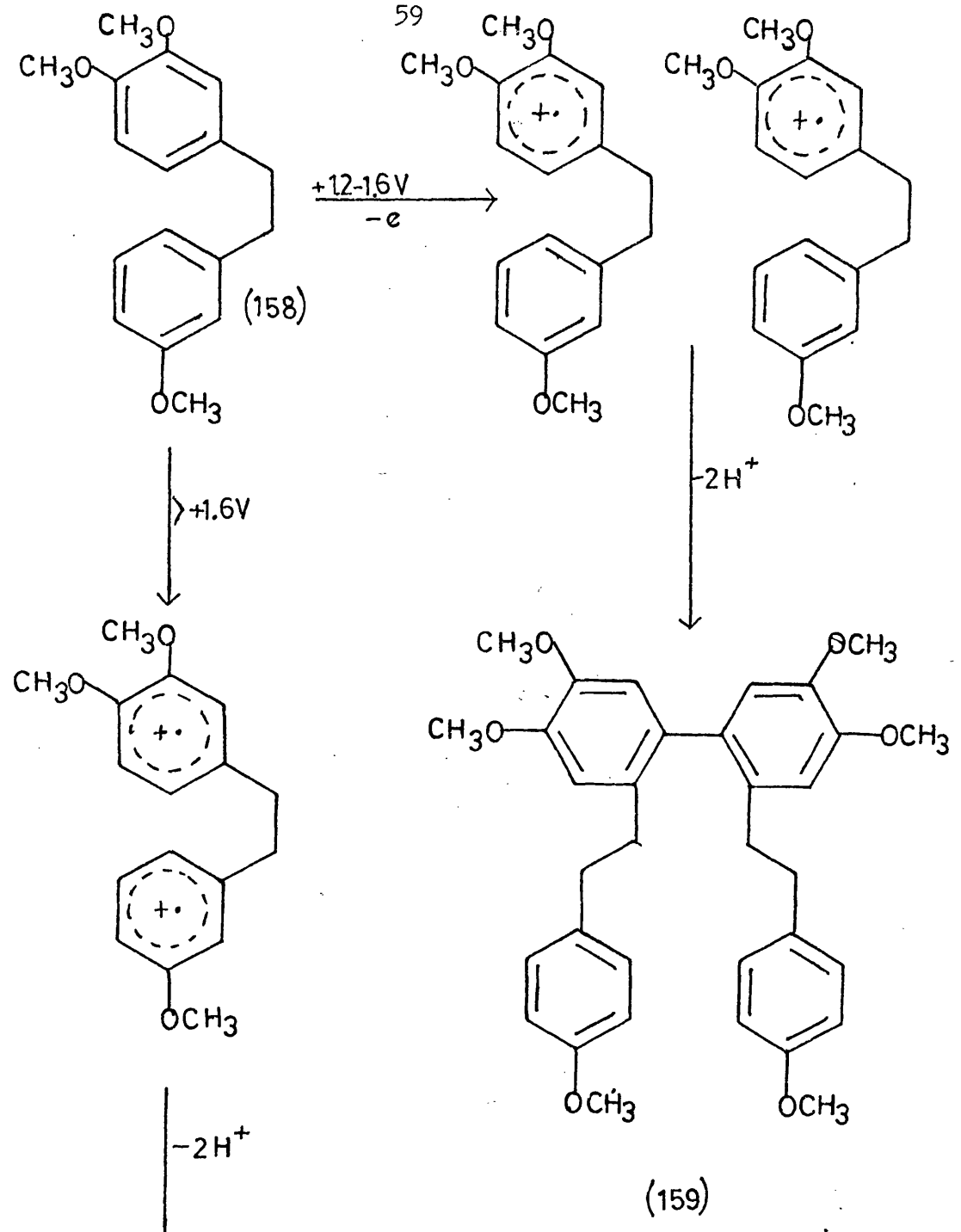
The strongest evidence for the first mechanism rests on the observation that the anodic oxidation of 3,3',4-trimethoxybibenzyl(158) produced the intermolecularly coupled product (159) at low current density (3×10^{-5} Acm^{-2}) but at higher current density (0.1 Acm^{-2}) a small quantity of the intramolecularly coupled product(160) was also formed, albeit in low yield(1.5%)[144]. The cyclic voltammogram of the compound shows peaks at 1.2V and 1.6V *versus* SCE, corresponding to the oxidation of the dimethoxylated and monomethoxylated rings respectively. It would be expected therefore, if the first mechanism (Scheme I) were operating, that at potentials between 1.2Vand 1.6V intermolecular coupling would take place exclusively as only one ring on each molecule would



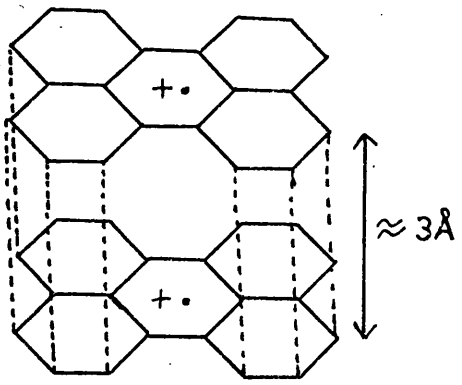
Scheme I



Scheme II

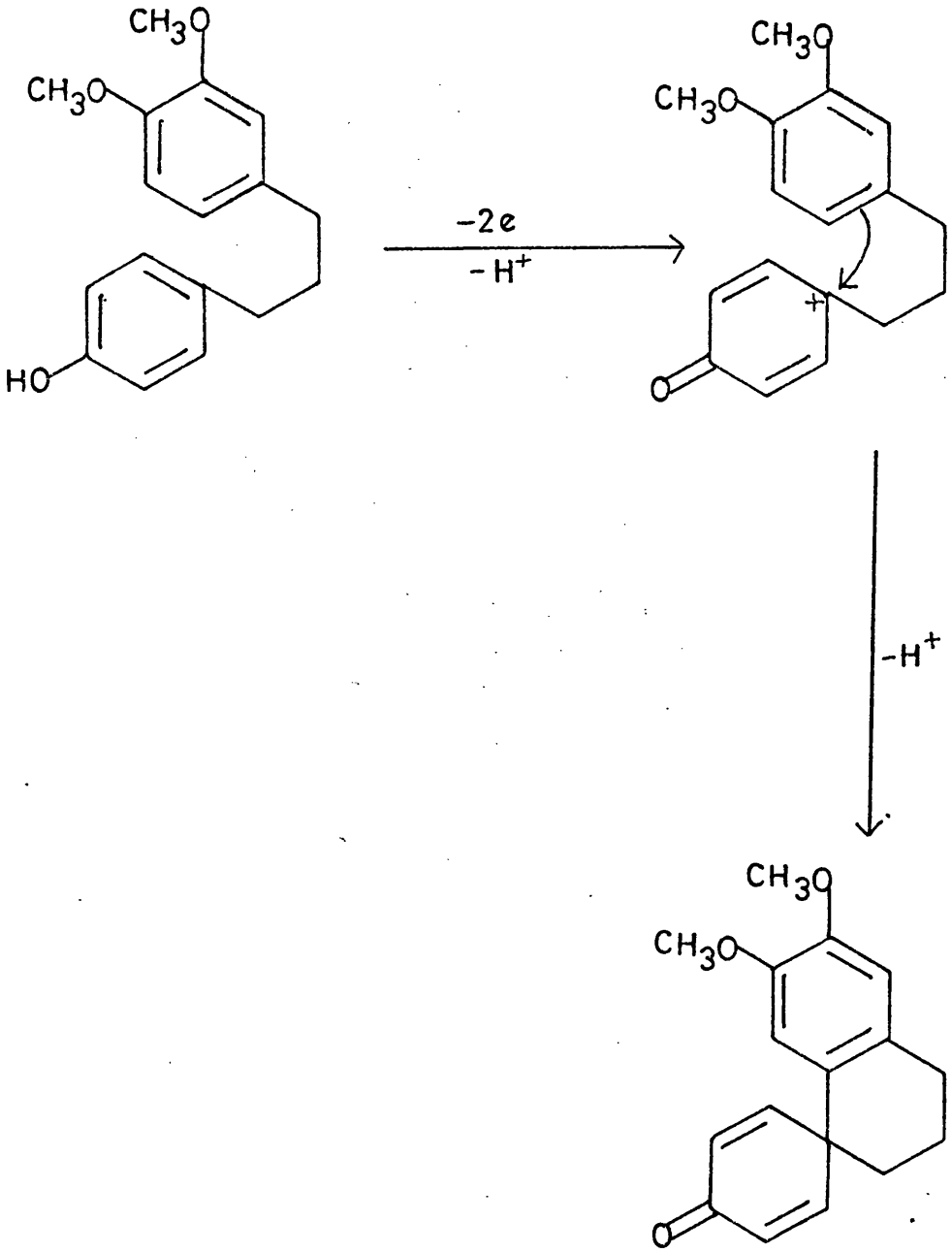

CH3O
CH3O
OCH3
(158)
+1.2-1.6V
-e
+1.6V
-2H+
(159)
(160)

exist as a radical cation. At potentials greater than 1.6V intramolecular as well as intermolecular coupling should take place as both aryl rings are now in the oxidised form. Unfortunately the potentials at which the oxidations were performed were not reported but the evidence for the mechanism is still reasonably strong. Nevertheless the diradical dication mechanism involves the approach of two positively charged species which at first sight seems unlikely; there is however evidence that the mutual attraction of the two radicals to some extent overcomes the electrostatic repulsion[147]. Perylene radical cations, for instance, are known to exist as dimers(161)[148].



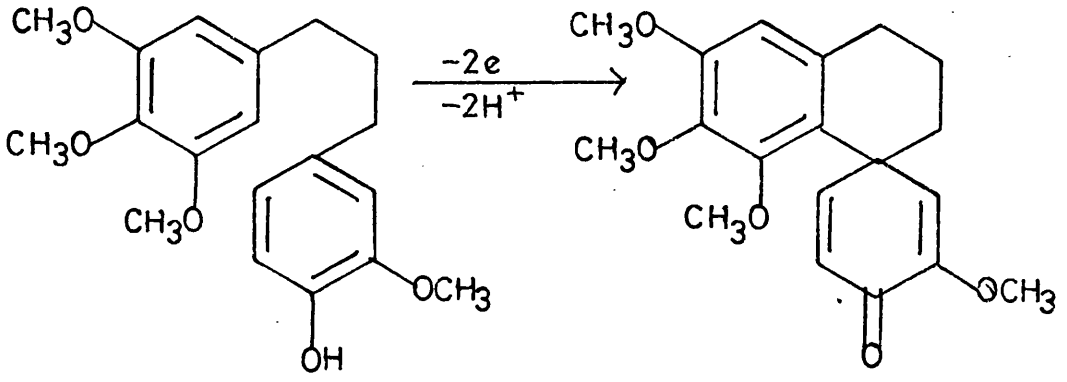
(161)

Ion pairing may also help to reduce repulsion by reducing the effective positive charge on the aryl rings[147,149]. Another reaction mechanism which has been put forward for a particular reaction may also have some general applicability where phenolic aryl rings are involved (Scheme III)[151]. The

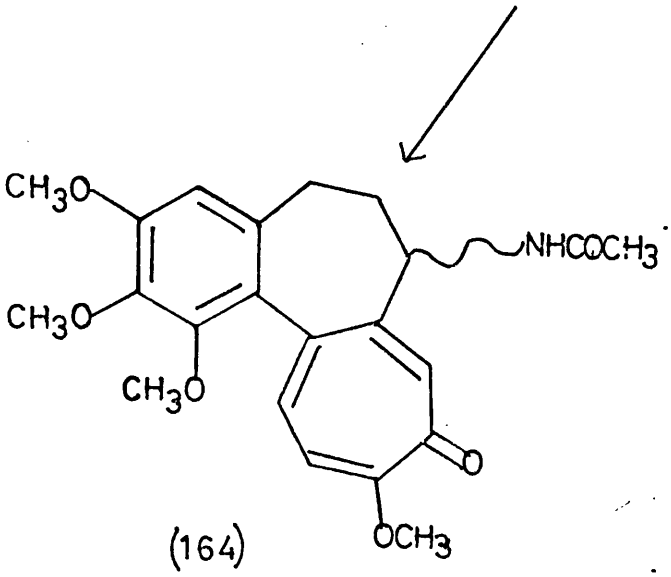


Scheme III

facile loss of the phenolic proton forces coupling para to the hydroxyl function, even when other electron donating groups are present. Kotani[152] has used this principle in the synthesis of (±) colchine(164), thus coupling to the more hindered position of the 3-methoxy-4-hydroxyphenyl moiety of the diaryl propane(162) leads to the formation of the desired dienone(163).



(162) (163)

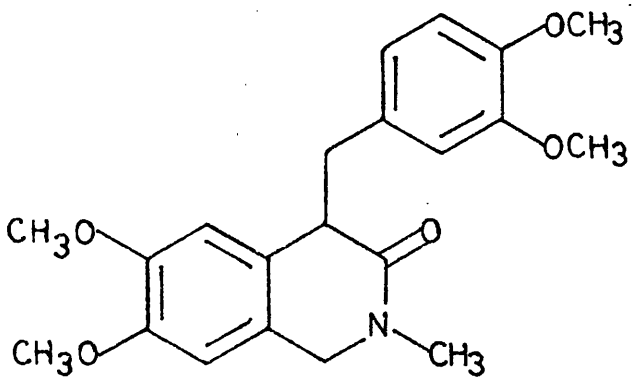


(164)

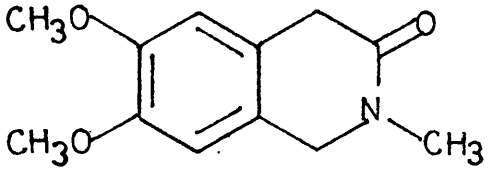
DISCUSSION

Routes to 4-Substituted 1,4-Dihydro-3(2H)-isoquinolinones.

From the results of the successful cyclisation of the lactone(4a) the obvious initial target compound for study was judged to be 1,4-dihydro-6,7- dimethoxy-4-(3,4-dimethoxy-benzyl)-2-methyl-3(2H)-isoquinolinone(4b). The method chosen to prepare this compound was that used by Brossi[16] and subsequently modified by Wyatt[7] and Maskell[153] (Scheme IV) to synthesise the parent compound 1,4-dihydro-6,7-dimethoxy-2-methyl-3(2H)-isoquinolinone(165). (See introduction p.20)

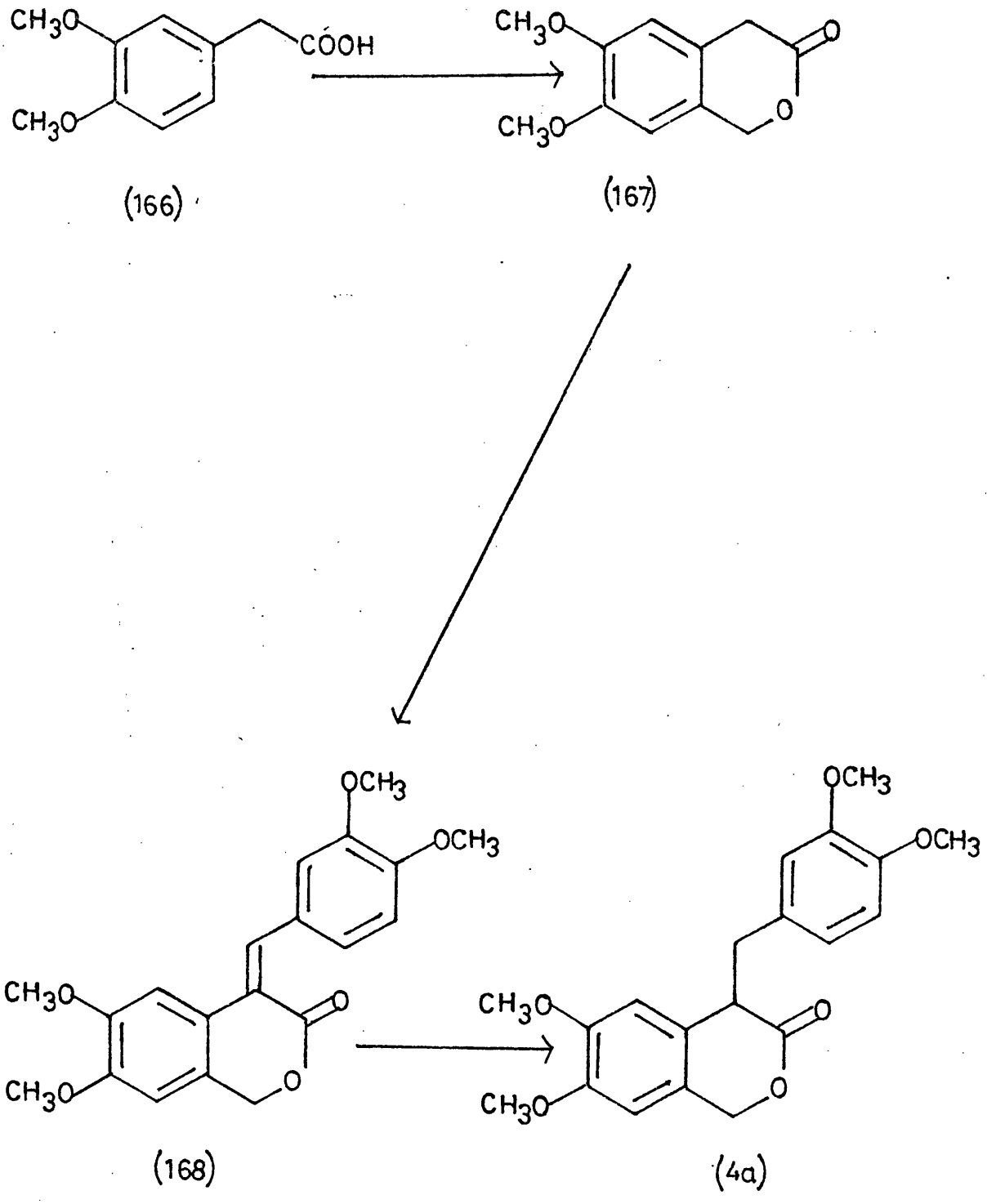


(4b)



(165)

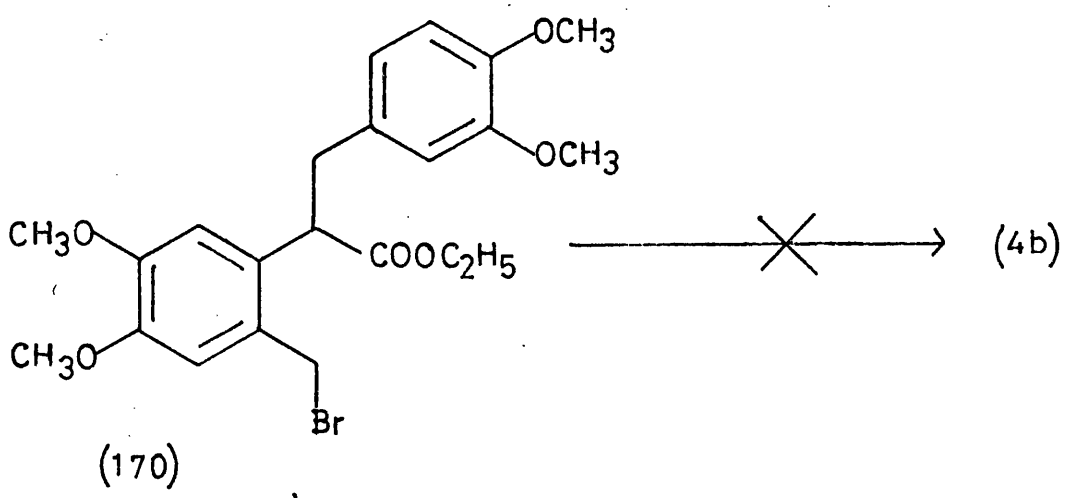
Thus the isochromanone(167) was prepared by treating 3,4-dimethoxyphenylacetic acid(166) with formaldehyde and hydrochloric acid. A condensation between this compound and 3,4-dimethoxybenzaldehyde in the presence of piperidine produced 6,7-dimethoxy-4-(3,4-dimethoxybenzylidene)-3-isochromanone(168) in good yield and catalytic reduction of this afforded 6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-3-isochromanone (4a). This compound was treated with hydrogen bromide in absolute ethanol to form ethyl 2-(2-bromomethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionate(170) which was found to be both light and moisture sensitive. This was treated with ethanolic methylamine in the presence of anhydrous potassium carbonate but the resulting colourless solid exhibited signals due to only four aromatic protons in its ^{1}H n.m.r. spectrum and could not therefore be the required isoquinolinone(4b). It was found that the same product could be obtained by treatment with anhydrous potassium carbonate but not on merely standing in ethanol. Eventually it was identified as 5-carbethoxy-2,3,8,9-tetramethoxy-dibenzo [b,f] cycloheptane(171). In an attempt to alter the course of this reaction in favour of the desired isoquinolinone the reaction conditions were varied. In particular the temperature at which the reaction took place was reduced. None of these variations was successful in deflecting the cyclisation to a lactam instead of to a cycloheptane derivative. Isolation of both geometrical isomers of the benylidene compound(168) is possible and they may be purified by means of fractional crystallisation and stuctural assign-



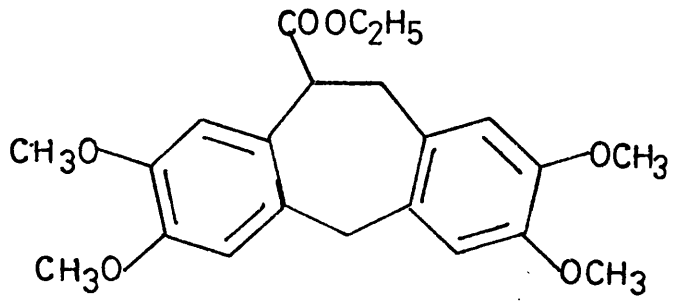
(166) (167)

(168) (4a)

Scheme IV



(170)



(171)

Scheme IV continued

ments follow from ^{1}H n.m.r. evidence (p.151). The aromatic region of the spectra are reproduced below.

In fig 1 a typical 1,2,4-trisubstitution pattern can be discerned:-

δ7.78	doublet	J= $2H_3$ proton	c
δ7.31	doublet of doublets	J= 2 and $7H_3$ proton	b
δ6.85	doublet	J= $7H_3$ proton	a

In fig 2, the same pattern, though less clear, can still be seen:-

δ7.11	doublet	J= $2H_3$ proton	c
δ7.15	doublet of doublets	J= 2 and $8H_3$ proton	b
δ6.82	doublet	J= $8H_3$ proton	a

The remaining three protons may be assigned by considering the shift of the peaks in changing the solvent from deuteriochloroform to deuteriobenzene. Connolly and McCrindle [154,155] have evolved a general rule for the prediction of such effects by considerating a reference plane 'P' perpendicular to the plane of the carbonyl group (figs 1 and 2). All protons to the right of this plane would experience a downfield shift and all those to the left and upfield shift. For convenience the authors define a quantity Δ thus:-

$$\Delta = \delta_{CDCl_3} - \delta_{Ar}$$

i.e. protons to the left of the plane 'P' have positive Δ values and those to the right negative Δ values. The effect is smallest near to the plane, rises rapidly to a maximum with increasing distance and then begins to decrease. As protons d and e are to the left of the plane in both cases they would have positive Δ values (see table 1) whilst proton f

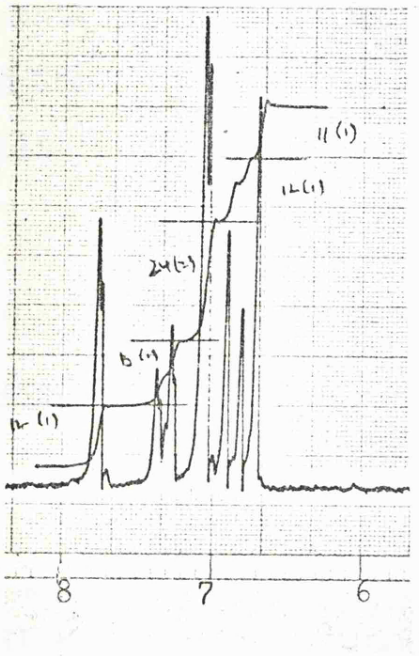
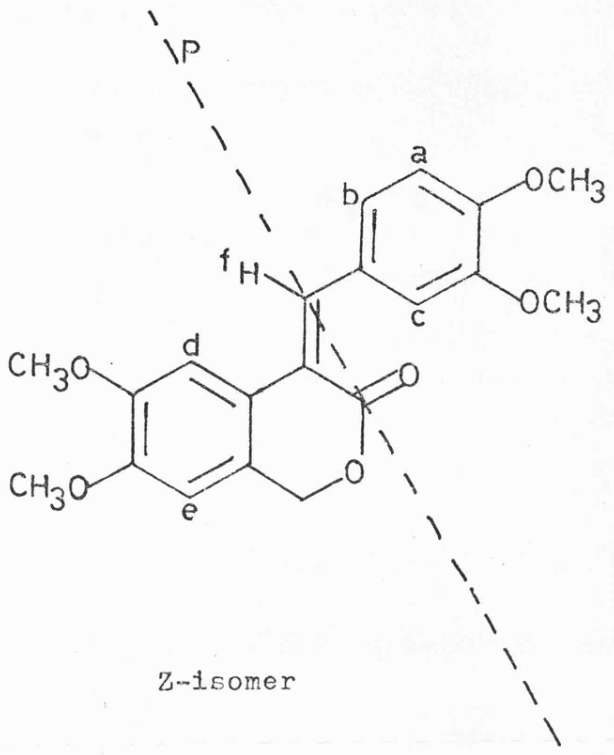


fig. 1(90 MHz, $CDCl_3$)



Z-isomer

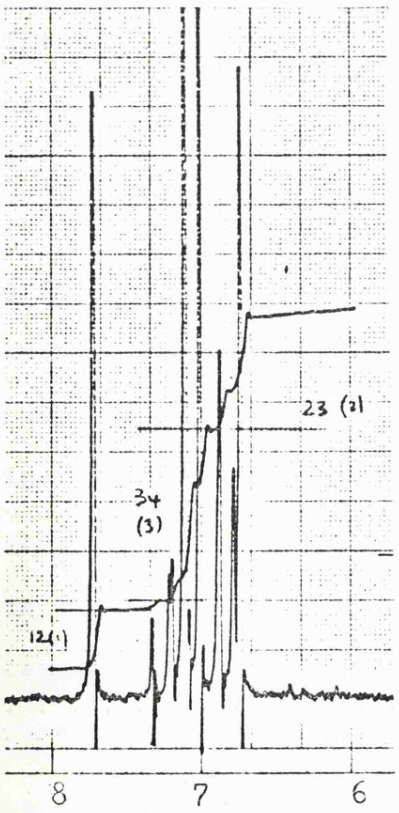
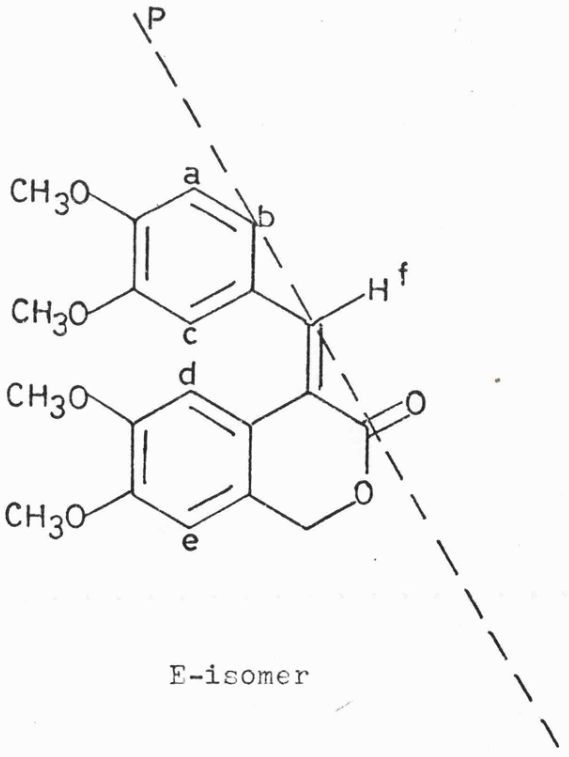


fig. 2(90 MHz, $CDCl_3$)



E-isomer

would have a positive value in the Z-isomer but negative in E-isomer. The remaining assignments can be made as follows:-

fig. 1

δ7.08, δ7.03	two singlets	protons f and e
δ6.70	singlet	proton d

fig. 2

δ7.71	singlet	proton f
δ7.01	singlet	proton e
δ6.74	singlet	proton d

It will be noted that proton e has a Δ value of about zero in both cases , a situation attributed to its remoteness from the plane 'P' ($\approx 5\overset{o}{A}$) compared with proton d ($\approx 2.4\overset{o}{A}$). This evidence is the basis of the tentative differentiation between protons d and e given in the above argument. In the Z-isomer proton f is very close to the plane 'P', whereas it is appreciably further away in the E-isomer. Thus the greater magnitude of the modulus of the Δ value in the E-isomer would be expected. In the Z- isomer protons a,b,and c would all be expected to have negative Δ values whereas in in the E-isomer they would be expected to have Δ values of about zero as they are all rotating through the plane 'P'. In fact proton a has a significant postive value in both cases. This cannot be explained by this theory and leaves some ambiguity about the assignments given.

Table 1

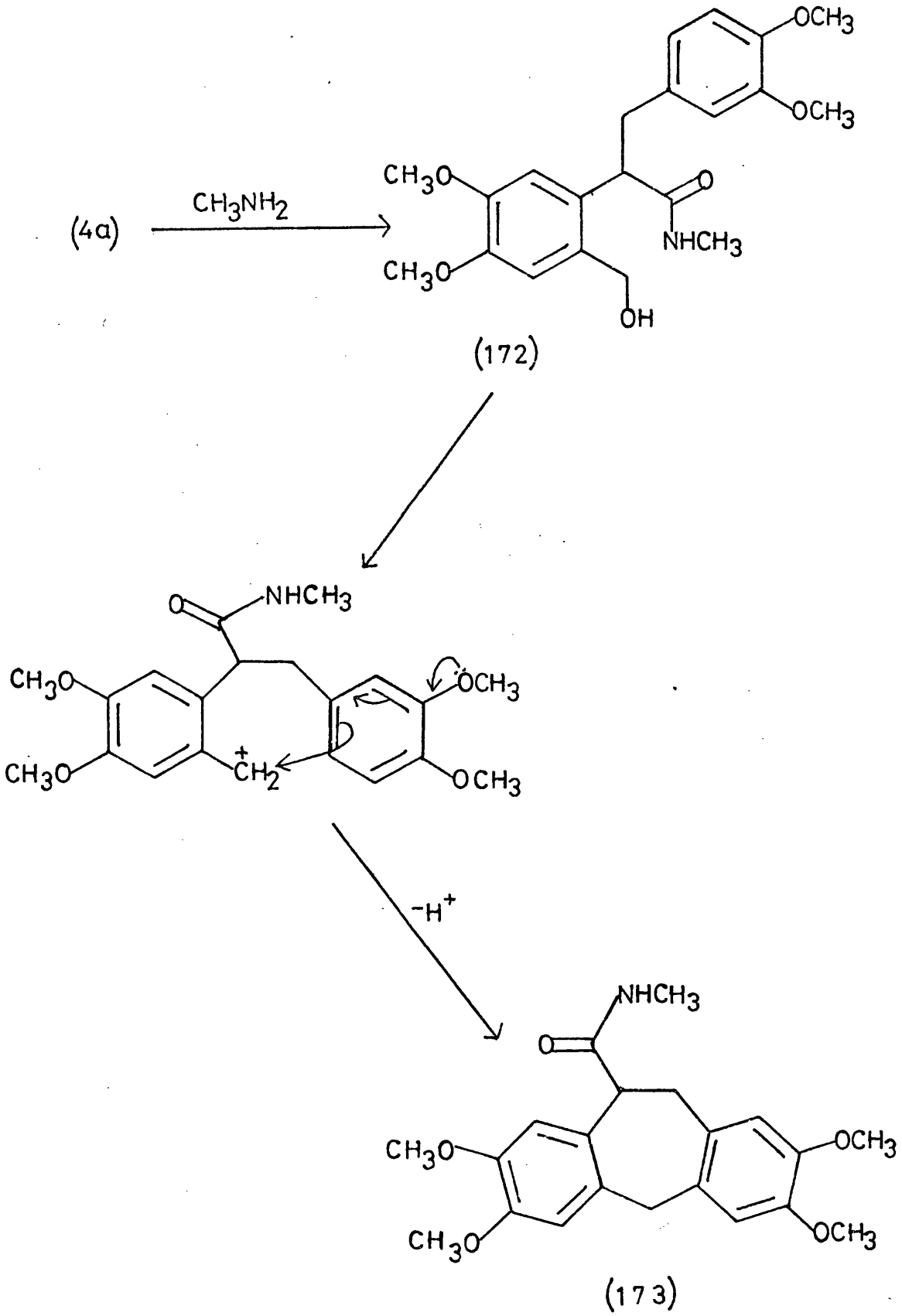
Proton as assigned	δ_{CDCl_3}	$\delta_{C_6H_6}$	$\Delta(\delta_{CDCl_3} - \delta_{C_6H_6})$
fig 1			
a	6.85	6.62	+ 0.23
b	7.31	7.50	- 0.19
c	7.78	8.13	- 0.25
d	6.70	6.18	+ 0.52
e	7.05*	7.05	0
f	7.05*	6.87	+ 0.18
fig 2			
a	6.82	6.44	+ 0.38
b	7.15	7.06*	+ 0.09
c	7.11	7.06*	+ 0.05
d	6.74	6.25	+ 0.49
e	7.01	7.06*	+ 0.05
f	7.71	8.05	- 0.34

*approximate value for comparison only

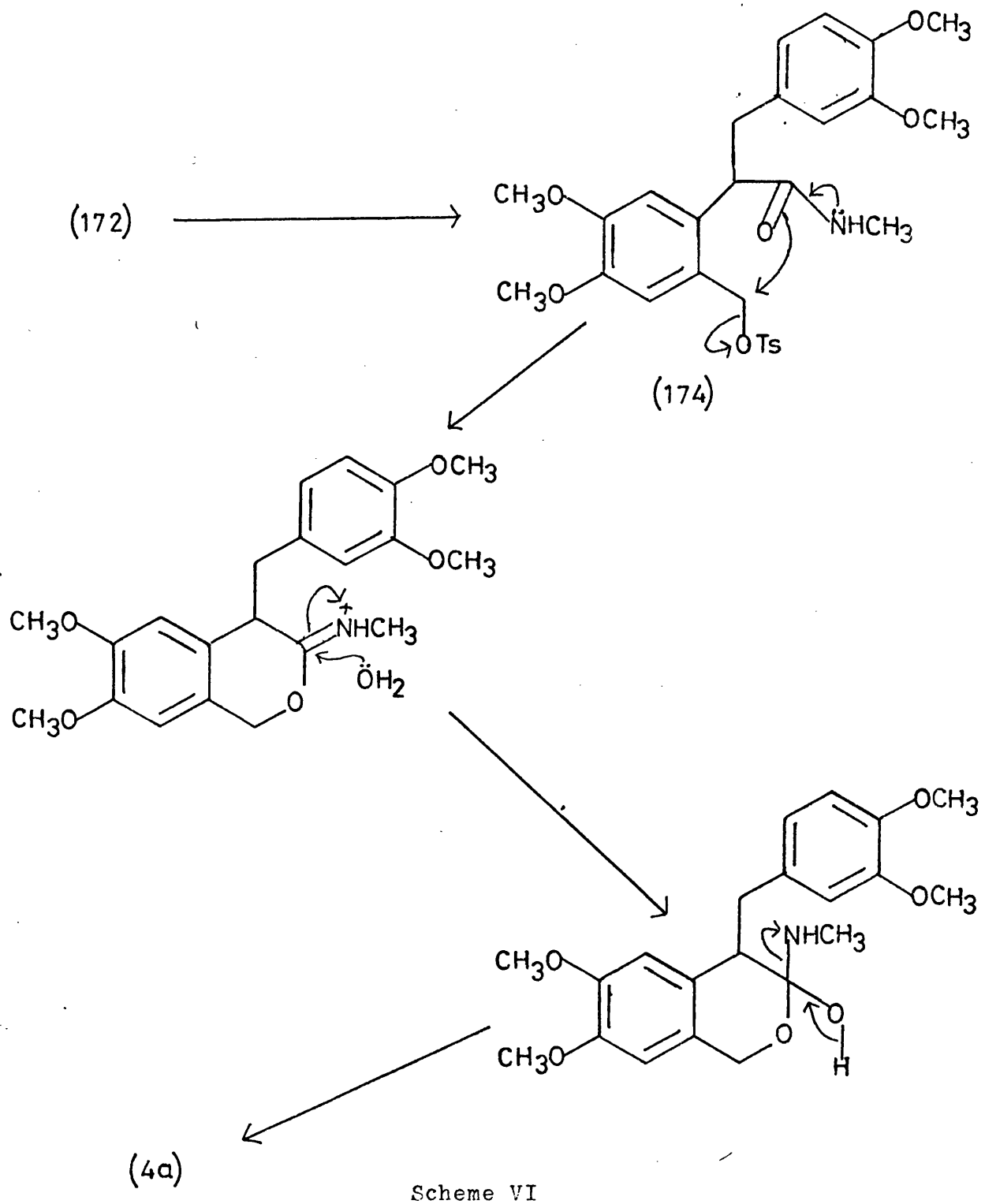
This leads to the interesting conclusion that the major product of the reaction is the E-isomer which it would be expected would be the least thermodynamically stable of the two. This implies that the products of the reaction are kinetically controlled which is further borne out by ^1H n.m.r. studies of crude reaction mixtures which show the product ratio to be consistent at about 2:1, E:Z from ten minutes

after the start of the reaction until its completion. These results are confirmed by high performance liquid chromatography analysis which reveals the isomer ratio (E:Z) in the reaction mixture after two hours at 130°C to be 2:1 (see experimental section for details). However, on heating to 170°C for one hour the isomer ratio changes to 1.25:1, showing an increase in the proportion of the supposed thermodynamic favoured product. There are, however, other products formed during this heating and it is possible that the change in isomer ratio may be due to differential rates of decomposition. There is insufficient evidence to draw any further conclusions about the course of the reaction.

Treatment of the isochromanone (4a) with methylamine affords N-methyl-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide(172)[156] which it was hoped would dehydrate to form the isoquinolinone(4b). Unfortunately the alcohol remains unchanged after heating to 200°C or upon heating under reflux conditions in benzene containing p-toluenesulphonic acid. However, upon treatment with either ethyl polyphosphoric ester (PPE) or phosphoric oxide 2,3,8,9-tetramethoxy-5-(N-methylformamido)-dibenzo[b,f]cycloheptane(173) was formed, presumably by the mechanism outlined in Scheme V. If the hydroxyl group were replaced by a better leaving function it was thought that a concerted displacement by nitrogen would be more likely to take place if conditions were sufficiently mild and an attempt was made to prepare the tosylate(174). No reaction occurs between the alcohol and p-toluenesulphoyl chloride in pyridine at room temperature


(4a)
CH_3NH_2
CH_3O
CH_3O
OCH_3
OCH_3
O
$NHCH_3$
OH
(172)
$NHCH_3$
O
CH_3O
CH_3O
OCH_3
OCH_3
$\overset{+}{C}H_2$
$-H^+$
$NHCH_3$
O
CH_3O
CH_3O
OCH_3
OCH_3
(173)

Scheme V


(172)
OCH3
OCH3
CH3O
CH3O
NHCH3
O
OTs
(174)
OCH3
OCH3
CH3O
CH3O
NHCH3
ÖH2
O
OCH3
OCH3
NHCH3
CH3O
CH3O
O
O
H
(4a)

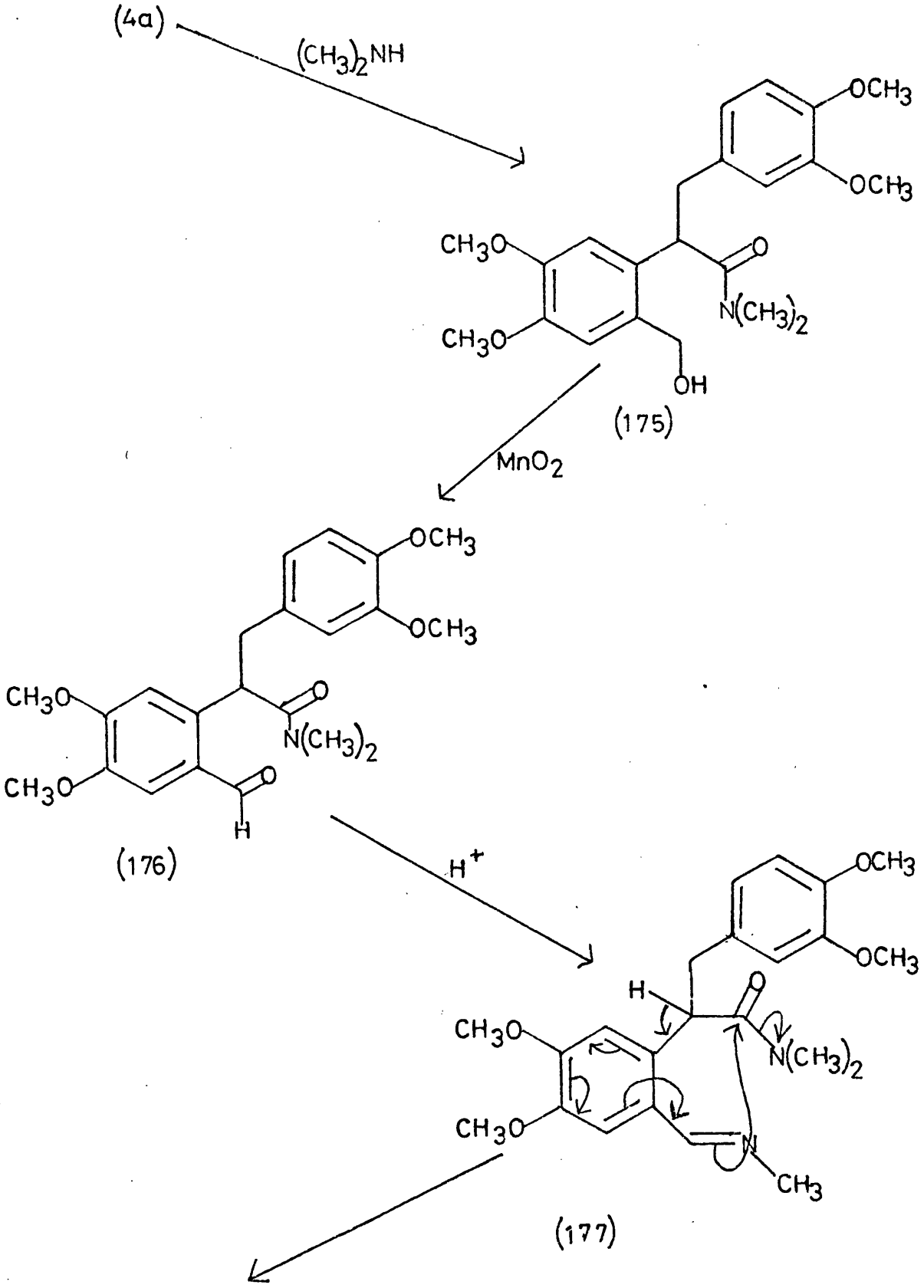
Scheme VI

but on heating the isochromanone (4a) is formed, showing that the oxygen rather than the nitrogen atom of the amide function displaces the p-toluenesulphonate ion from the intermediate ester (Scheme VI). The synthesis was then attempted using the silver tosylate method[157], but treatment of the alcohol with thionyl chloride followed by addition of silver tosylate solution resulted, once more, in the formation of the dibenzocycloheptane(173) presumably *via* formation of a carbonium ion through the abstraction of chloride ion by silver cation.

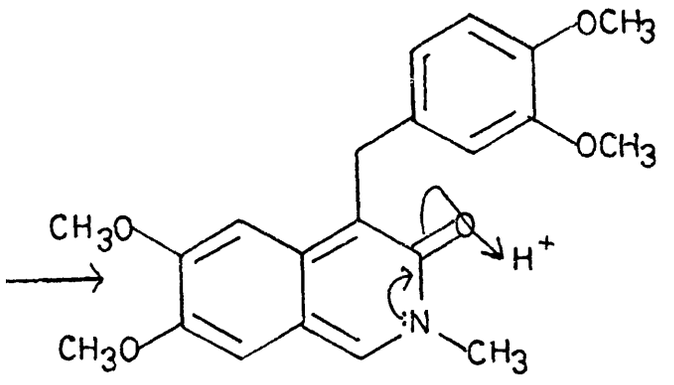
As it seemed unlikely that an approach *via* the amido-alcohol(172) would be successful, attention was turned to the method of McCorkindale[39] previously discussed in the introduction (p.23). The application of this method to the synthesis of the isoquinolinone in question (Scheme VII) had previously been attempted by Patterson[158] who had been unable to isolate a pure product from the reduction of the salt(179) but had not attempted to reduce the free base(180). The free base, although unstable, was isolated in good yield but attempts to reduce it catalytically under a variety of conditions led to multicomponent mixtures which were inseparable by preparative thin layer chromatography.

Many of the intermediates in Scheme VII had not previously been fully characterised. These omissions have now been put right and salient spectral and analytical data are to be found in the experimental section of this thesis.

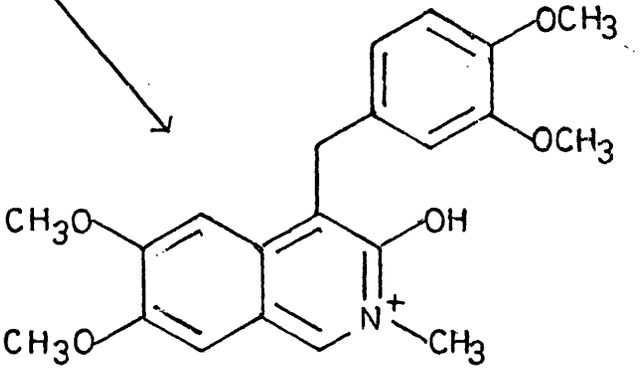
Reduction of the imine(177), followed by cyclisation would lead directly to the 1,4-dihydro-3(2*H*)-isoquinolinone(4b).


(4a)
$(CH_3)_2NH$
OCH_3
OCH_3
CH_3O
CH_3O
O
$N(CH_3)_2$
OH
(175)
MnO_2
OCH_3
OCH_3
CH_3O
CH_3O
O
$N(CH_3)_2$
O
H
(176)
H^+
OCH_3
OCH_3
H
O
CH_3O
CH_3O
$N(CH_3)_2$
N
CH_3
(177)

Scheme VII

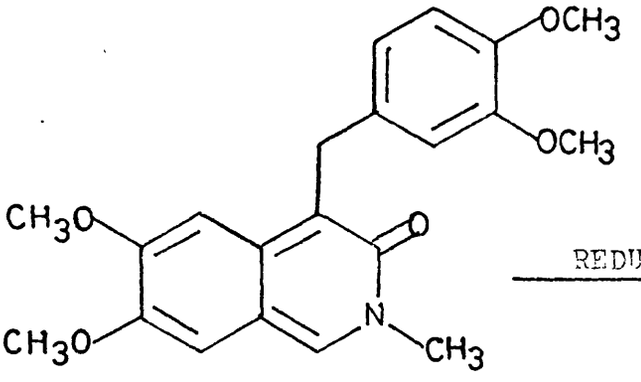


(178)



(179)

NH_4OH



(180)

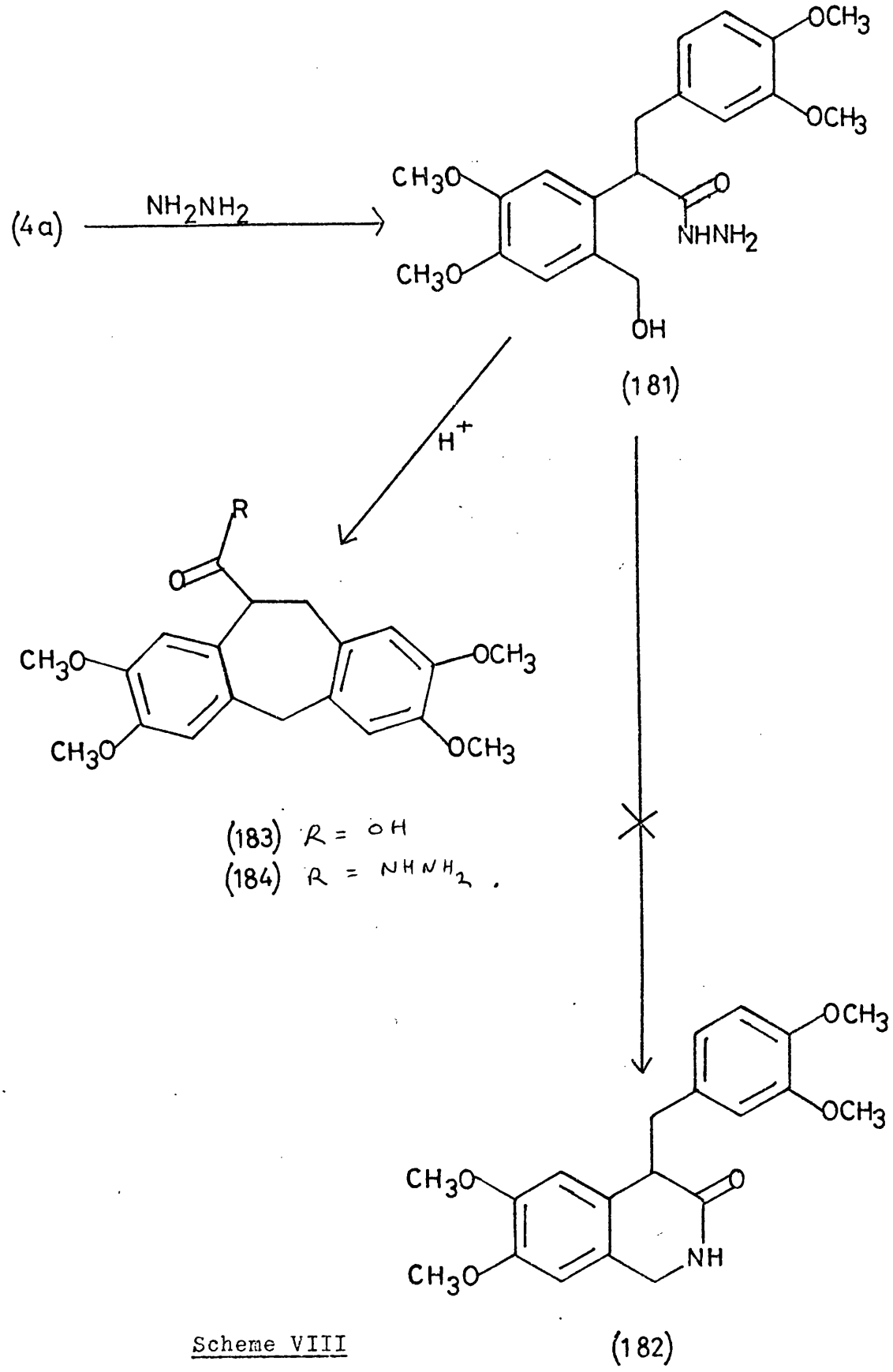
REDUCTION → (4b)

Scheme VII continued

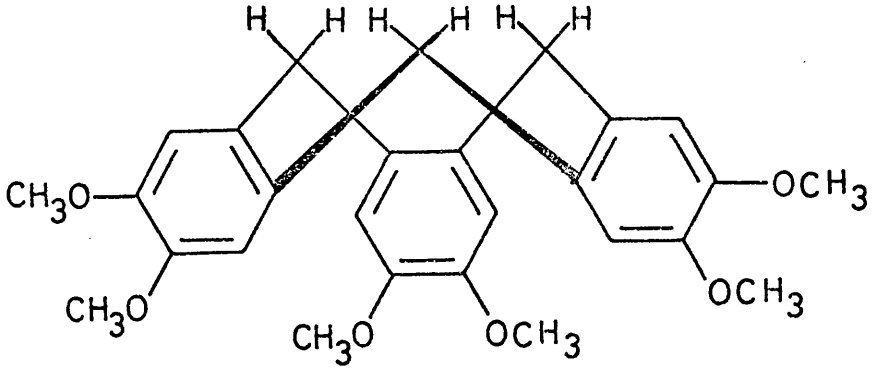
However, sodium borohydride reduction of the crude imine led to a mixture of products which could not be resolved. Hydrogenation of the aldehyde(176) in ethanolic methylamine gave an identical mixture. It is probable that the amine was produced but that it decomposes rapidly in air.

Consideration was then given to the method of Rosen and Popp[37] (introduction p.21) which might enable the N-dimethyl-isoquinolinone(182) to be synthesised (Scheme VIII). This compound could then be methylated using sodium hydride and methyl iodide[159]. The hydrazide(181) was synthesised in good yield by treatment of the isochromanone (4a) with hydrazine hydrate, but, on treatment with dilute hydrochloric acid, the carboxylic acid(184) is formed or, if the treatment is terminated prematurely, the hydrazide(183). The latter compound is also produced upon treatment of the substrate with p-toluenesulphonic acid in benzene.

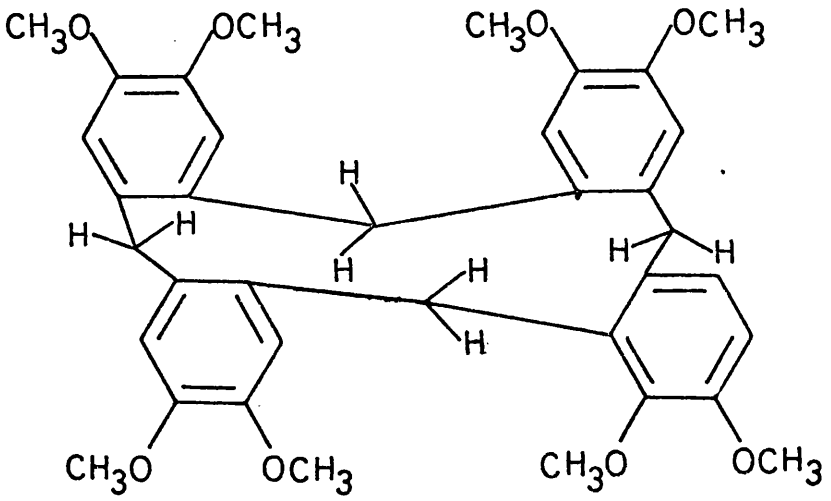
An alternative route to the desired isoquinolinone(4b) would be the alkylation of 1,4-dihydro-6,7-dimethoxy-2-methyl-3(2H)-isoquinolinone(187). This compound was synthesised by the method of Finkelstein and Brossi[16] (introduction p.21) as modified by Wyatt[7] and Maskell[153]. Wyatt had already shown that this compound when treated with lithium diisopropylamide (LDA) and ethyl iodide underwent alkylation at the 4-position and Maskell had subsequently tried the alkylation using 3,4-dimethoxybenzyl chloride. This resulted in the formation of cyclotriveratrylene(185) and cyclotetraveratrylene(186) with no evidence for the formation of any of the desired product.


(4a)
NH_2NH_2
CH_3O
CH_3O
O
$NHNH_2$
OH
OCH_3
OCH_3
(181)
H^+
R
O
CH_3O
CH_3O
OCH_3
OCH_3
(183) R = OH
(184) R = $NHNH_2$
CH_3O
CH_3O
O
NH
OCH_3
OCH_3
(182)

Scheme VIII

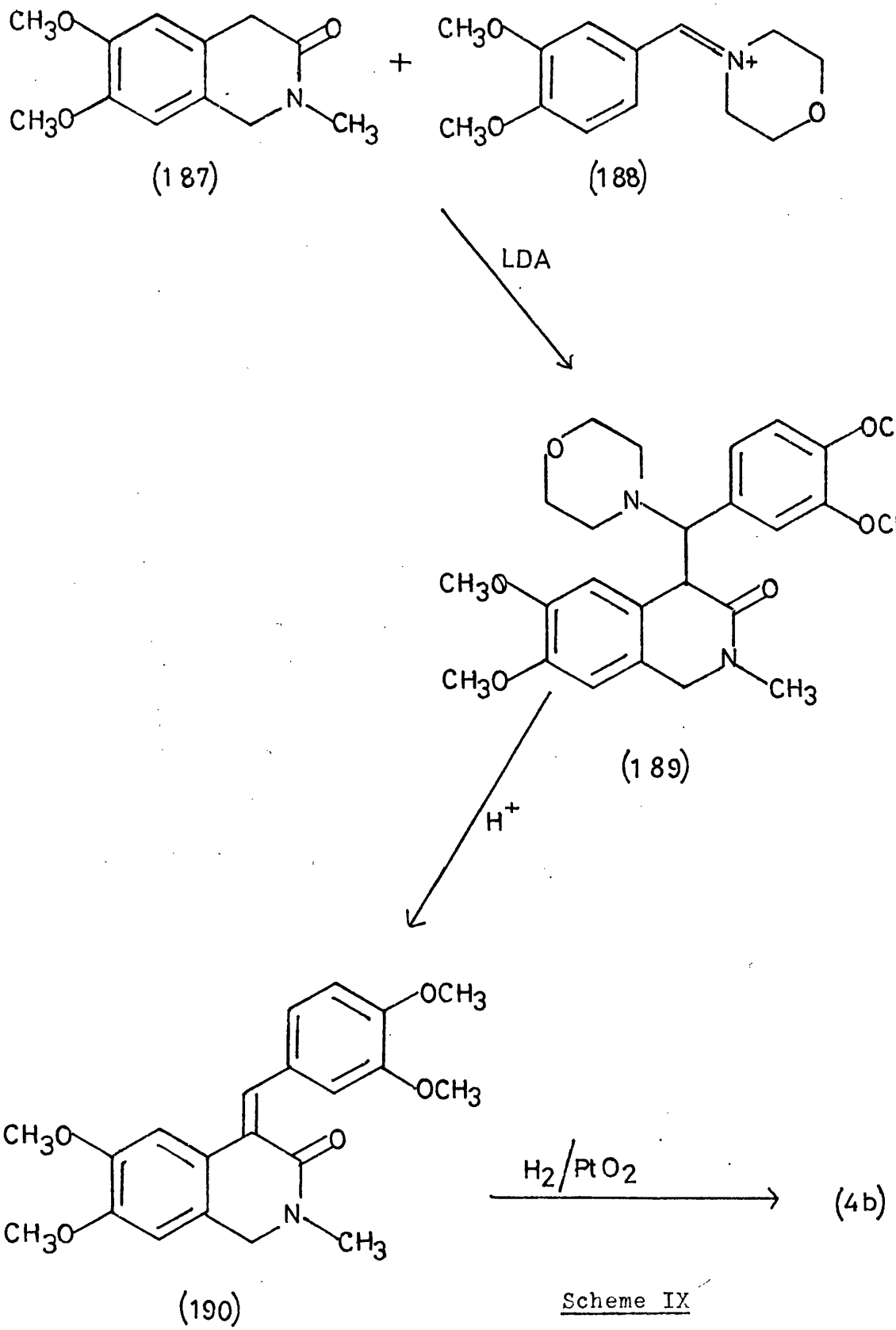


(185)



(186)

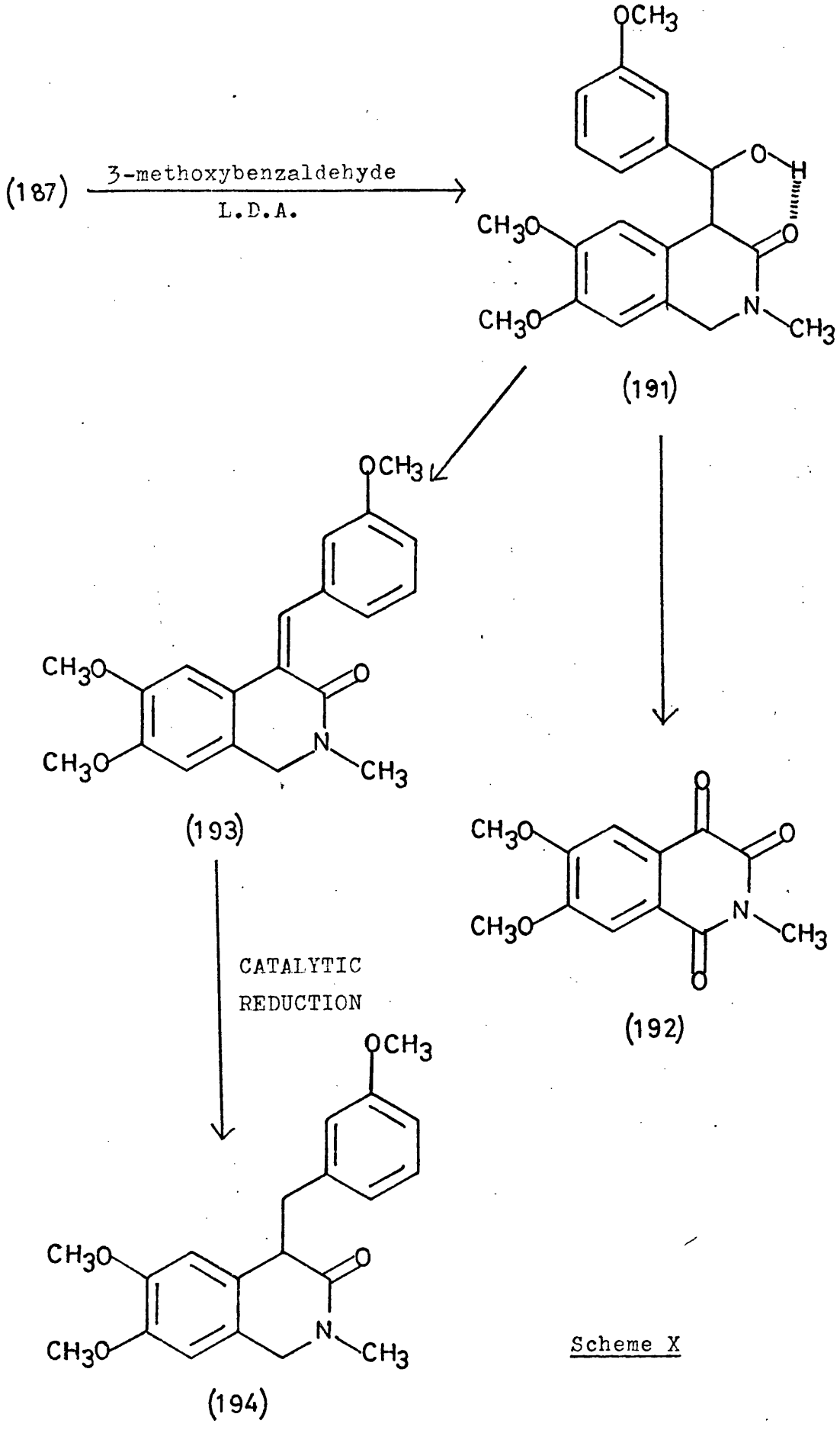
It was therefore decided to attempt the condensation of the isoquinolonone(187) with 3,4-dimethoxybenzaldehyde to form the corresponding benzylidene compound(190), followed by catalytic reduction to the isoquinolinone(4b). Unfortunately it was found that no reaction took place using lithium diisopropylamide at temperatures between -70°C and 0°C or using sodium hydride in boiling toluene. The perchlorate salt(188) was synthesised using the method of Leonard[160] by azeotropic elimination of water from a mixture of 3,4-dimethoxybenzaldehyde and morphine perchlorate. It was expected that the salt would be more susceptable to nucleophilic attack (Scheme IX) producing initially the compound (189) which when treated with acid would eliminate to form the benzylidene(190). However, upon treatment of the lactam with the salt in the presence of lithium diisopropylamide an inseparable mixture was produced.


CH3O
CH3O
O
N
CH3
(187)
+
CH3O
CH3O
N+
O
(188)
LDA
OCH3
OCH3
O
N
CH3O
CH3O
O
N
CH3
(189)
H+
OCH3
OCH3
CH3O
CH3O
O
N
CH3
(190)
H2/PtO2
(4b)

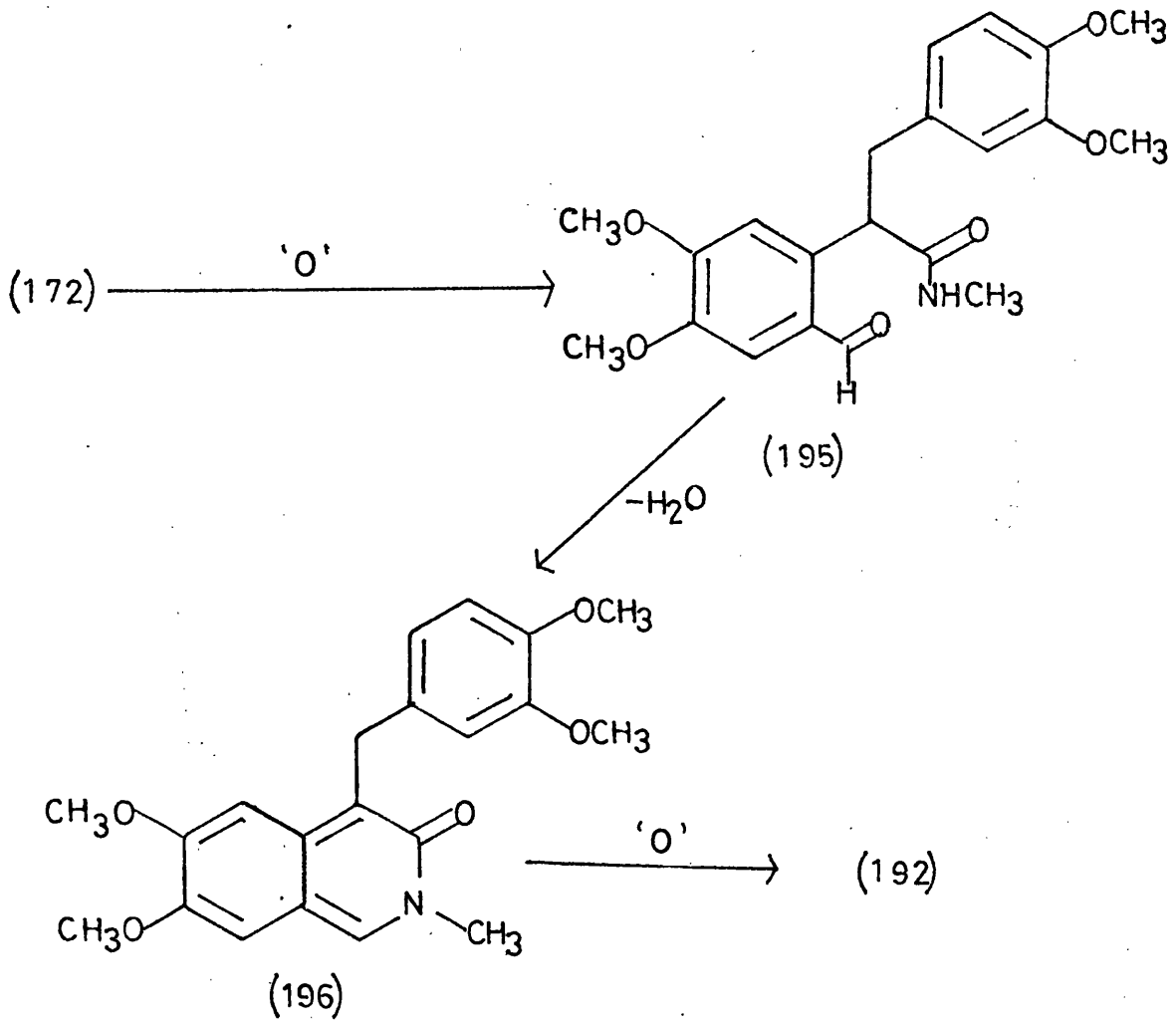
Scheme IX

1,4-Dihydro-6,7-dimethoxy-4-(3-methoxybenzyl)-2-methyl-3(2H)-isoquinolinone(194) is a suitable substrate for electrolysis because, although the oxidation potential of the substituent aryl ring would now be higher than that of the aryl ring fused to the heterocycle the correct positions would still be activated for the coupling reaction. Thus, as it was expected that 3-methoxybenzaldehyde would be more reactive than 3,4-dimethoxybenzaldehyde the lactam was treated with this aldehyde in the presence of lithium diisopropylamide. Attempts to recrystalise the resulting white precipitate led to the formation of a bright yellow compound identified as 6,7-dimethoxy-2-methyl-1,3,4-isoquinolinetrione (192). Purification of the original precipitate was effected by means of short column chromatography[161] and led to the isolation of 1,4-dihydro-4-(α-hydroxy-3-methoxybenzyl)-6,7-dimethoxy-2-methyl-3(2H)-isoquinolinone(191) as the major component. From the ^{1}H n.m.r. spectrum this appeared to be one diastereoisomer and although i.r. dilution studies evidenced the existence of intramolecular hydrogen bonding it was still not possible to completely define the stereochemistry. Treatment of this alcohol with p-toluenesulphonic acid in benzene or ethyl polyphosphoric ester or under hydrogenolysis conditions all led to the formation of the phthalonimide(192) and it was thus not possible to form the olefin(193).

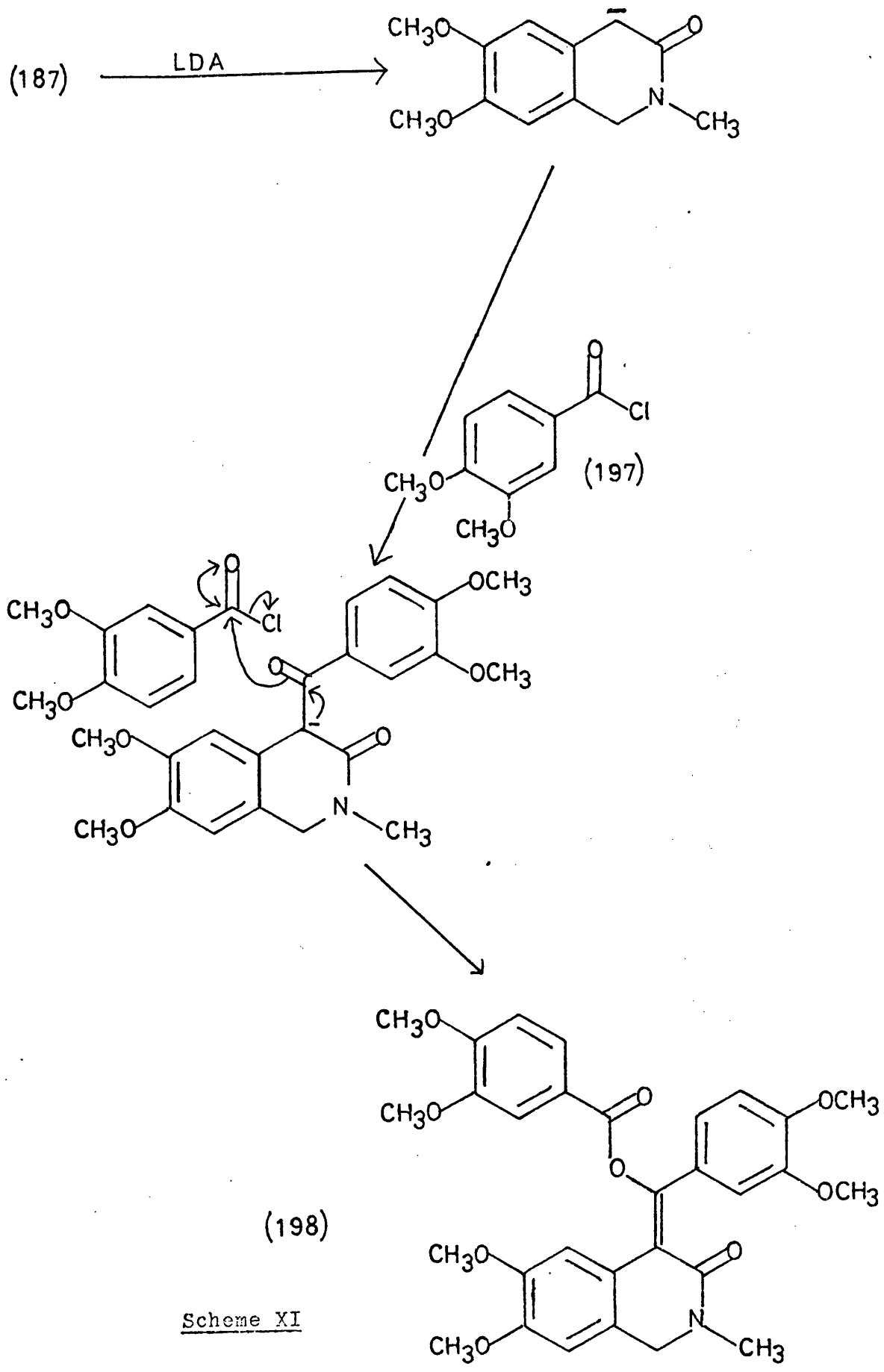
The same phthalonimide was formed by chromium trioxide oxidation of the amido-alcohol(172), probably via the 3(2H)-isoquinolinone(196) formed in turn from the aldehyde(195).


(187)
3-methoxybenzaldehyde
L.D.A.
OCH3
CH3O
CH3O
O
H
O
N
CH3
(191)
(193)
(192)
CATALYTIC
REDUCTION
(194)

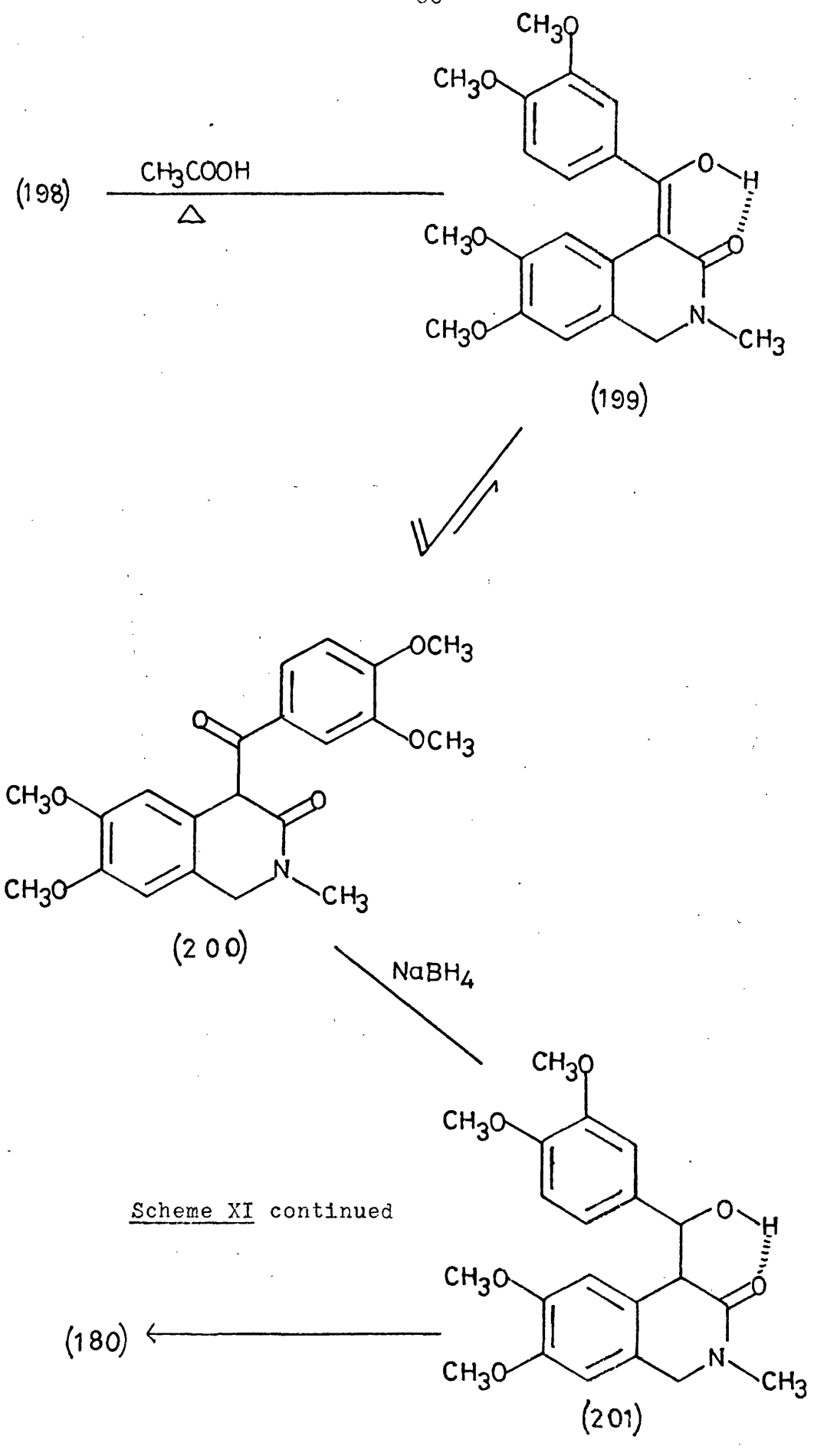
Scheme X



3,4-Dimethoxybenzoyl chloride(197) was found to react with the lactam(187) in the presence of lithium diisopropylamide to form 1,4-dihydro-6,7-dimethoxy-4-(3,4-dimethoxy-α-(3,4-dimethoxybenzoyloxy)benzylidene)-2-methyl-3(2H)-isoquinolinone(198) (Scheme XI). However, attempts to limit the reaction to one molar equivalent of acid chloride failed and ethyl 3,4-dimethoxybenzoate and p-nitrophenyl 3,4-dimethoxybenzoate failed to react with the lactam. Attempts to reduce the benzylidene function of the ester(198) have, so



Scheme XI



Scheme XI continued

far, been unsuccessful due largely to the insolubility of the substrate in the usual solvents, ethanol, ethylacetate, acetic acid etc.. Hydrolysis of the ester was extremely difficult for the same reason but it was eventually found that heating the ester under reflux conditions in glacial acetic acid for twelve hours produced 1,4-dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzoyl)-2-methyl-3(2H)-isoquinolinone(200). Interestingly, it would appear from the absence of an O-H peak and the presence of two carbonyl absorptions at 1645 and 1670 cm^{-1} in the i.r. spectrum of this compound (p.166) and the presence of a non-deuterable one proton singlet at $\delta 5.52$ in the ^{1}H n.m.r. spectrum (p.165) that this compound exists almost completely in the keto form(200) rather than the hydrogen-bonded enol form(199). The main reason for this is probably the destabilising effect of the steric interaction of the two aryl rings in the enol form. This together with the stabilisation gained by the conjunction of a carbonyl group with an aryl ring in the keto form must outweigh the gains made by the system from the hydrogen-bonding and conjunction of two aryl rings possible in the enol form.

This compound does not undergo either a Wolff-Kishner or a Clemmensen reduction to give (4b) directly and catalytic reduction, under a wide variety of conditions, was also unsuccessful. It may, however, be reduced with sodium borohydride to form 1,4-dihydro-4-(α-hydroxy-3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-3(2H)-isoquinolinone(201), which was shown by dilution studies of the i.r. spectrum to exhibit

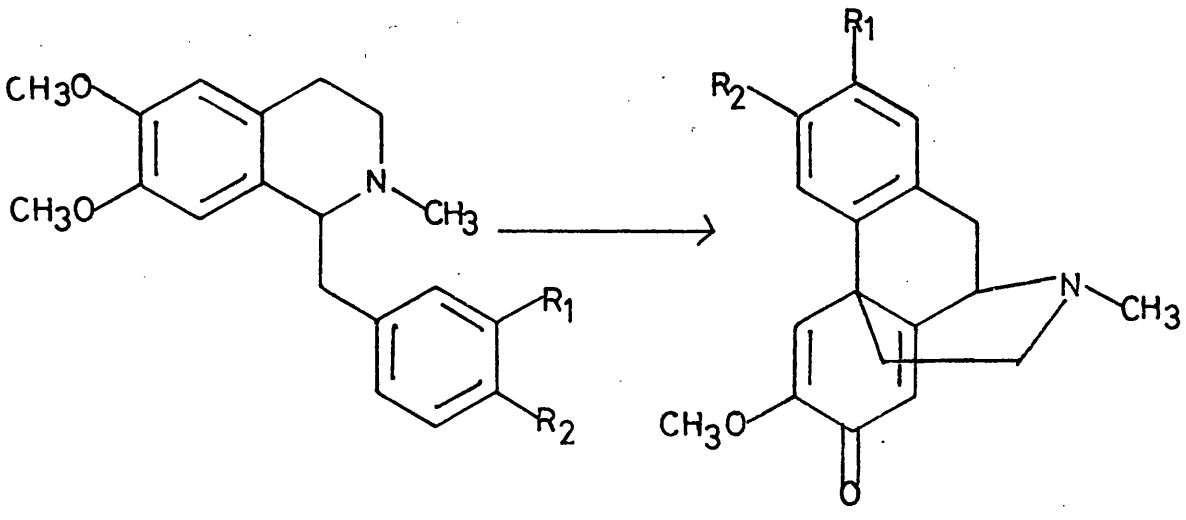
intramolecular hydrogen-bonding. The ^{1}H n.m.r. spectrum indicates that only one diastereoisomer is present and that this is the same isomer as that of the alcohol(191), but in contrast to that compound this alcohol seems to be relatively stable. It may be, for example, easily recrystallised from ethanol and it is expected that dehydration to the benzylidene compound(190) will be facile.

This reaction sequence was not developed further as in the work discussed above we noted 1,4-dihydro-6,7-dimethoxy-4-(α-hydroxy-3-methoxybezyl)-2-methyl-3(2H)-isoquinolinone (191) readily oxidised to the phthalonimide 6,7-dimethoxy-2-methyl-1,3,4-isoquinolinetrinone(192) even under the mildest conditions. Thus since we were hoping to oxidise the corresponding 3,4-dimethoxybenzyl compound(4b) in a fairly rigorous manner it seems that instead of aryl-aryl coupling, fragmentation etc. to the same product may occur. These conclusions coupled with the experimental difficulties related here, en route to the required substrate, caused us to question whether or not we had made the correct choice so we turned next to an alternative programme.

Electrochemical Oxidation and Preparation of 4-Substituted-1,2,3,4-Tetrahydroisoquinolines.

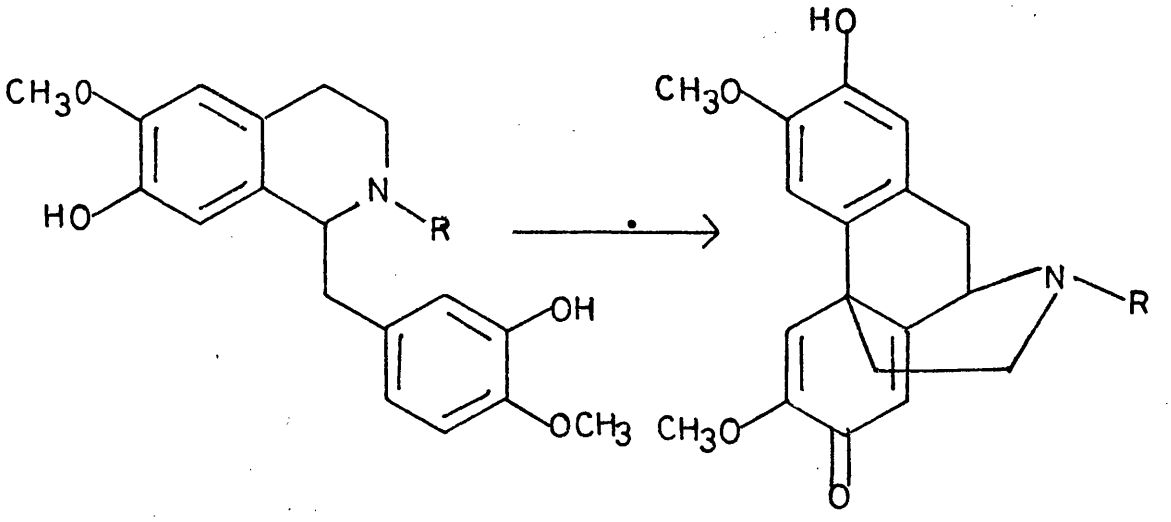
The next obvious route to an isomorphinandienone would be to oxidise a 4-benzyl-1,2,3,4-tetrahydroisoquinoline. Many examples of this are to be found in the literature, Kotani and Tobinaga[162] for example used electrochemical oxidation to form the morphinandienones(203) from the tetrahydroisoquinolines(202) and Bobbitt[163] using a similar technique was able to synthesise the compounds (205) and (204). Stermitz and Miller[164] reported that laudanosine(206) could be electrochemically oxidised to the morphinandieneone, (±)-O-methylflavinantine(207) at a potentialof 1.1V.

R_1, R_2= OCH_3, OAc, OH, OCH_2Ph and R_1R_2= OCH_2O.

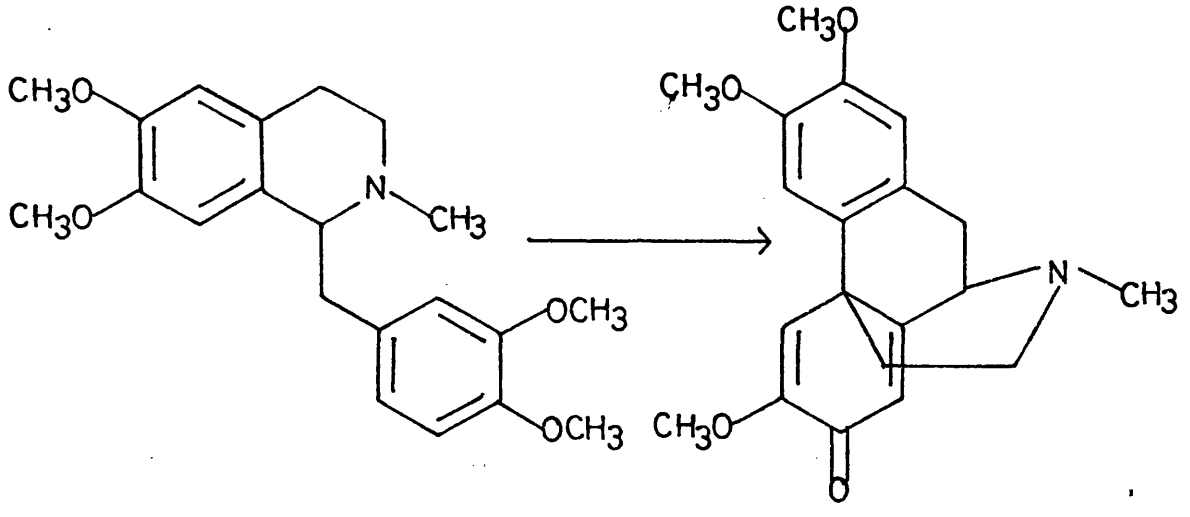


(202) (203)

R= H, CH_3, $COOC_2H_5$, $COCF_3$.



(204) (205)

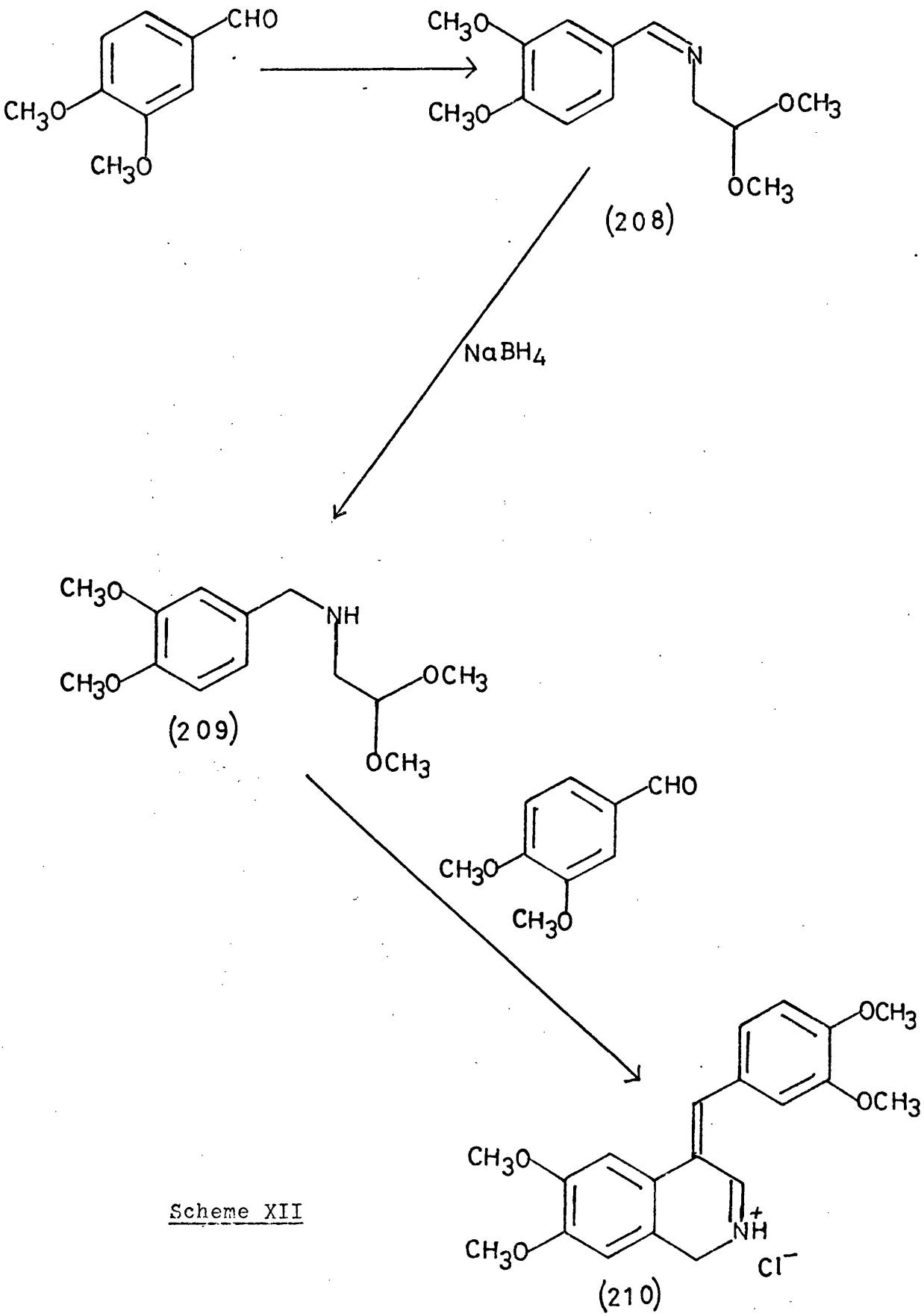


(206) (207)

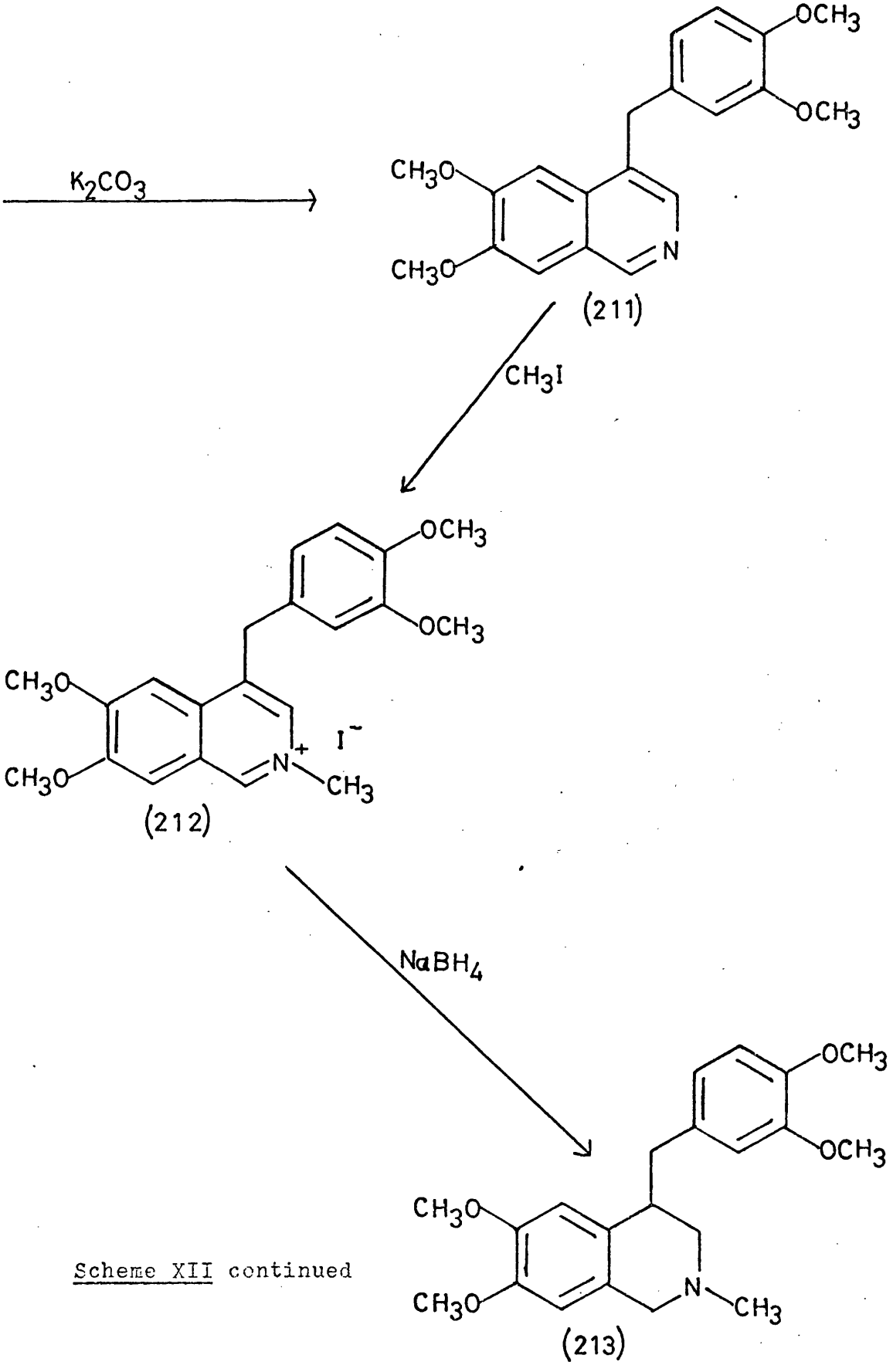
Thus it seemed that the obvious substrate to form an isomorphinandieneone on oxidation was 1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinoline (213). This was synthesised using the method of Bobbitt[110] (Scheme XII). The Schiff's base(208) was formed by azeotropic elimination of water from a mixture of 3,4-dimethoxybenzaldehyde and aminoacetaldehyde dimethylacetal. Reduction of the Schiff's base with sodium borohydride gave the acetal(209) which was then condensed with more 3,4-dimethoxybenzaldehyde in the presence of 6M hydrochloric acid to form the 1,4-dihydroisoquinolinium salt(210). Isomerisation of this salt by treatment with potassium carbonate in boiling ethanol resulted in the formation of 6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinoline(211). The methiodide of this compound was then reduced with sodium borohydride to produce the tetrahydroisoquinoline(213).

The conditions necessary for the isolation of the salt (210) were crucial. In particular it was mandatory to ensure that the immediate precursor(209) was sufficiently pure and that commercially available 3,4-dimethoxybenzaldehyde was recrystallised before use. After the reaction, however, it was not essential to isolate compounds (210) or (211) although a purer final product(212) was obtained if the intermediates were isolated and purified in sequence.

Unfortunately, the tetrahydroisoquinoline(213) did not give rise to a well defined cyclic voltammogram in acetonitrile containing sodium perchlorate, but showed only a broad anodic peak extanding from +0.5V to +1.2V (fig. 3, p.171).


CHO
CH3O
CH3O
CH3O
CH3O
N
OCH3
OCH3
(208)
NaBH4
CH3O
CH3O
NH
OCH3
OCH3
(209)
CHO
CH3O
CH3O
OCH3
OCH3
CH3O
CH3O
NH+
Cl−
(210)

Scheme XII



Scheme XII continued

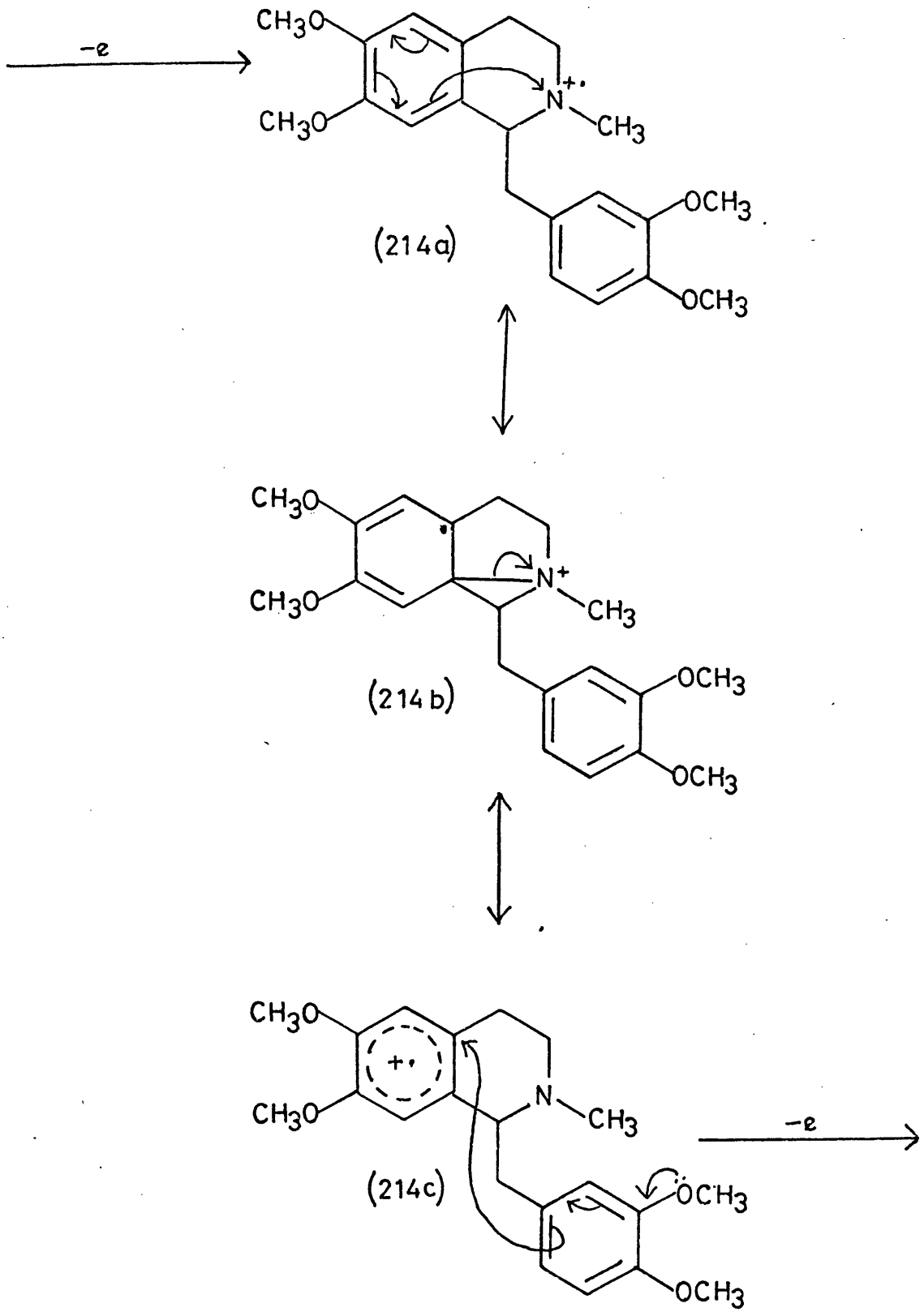
Preparative electrolyses using either platinum or carbon felt electrodes were difficult to control and had to be terminated prematurely because of electrode filming, a type of behaviour often encountered with benzylamines[165]. It is possible that initial oxidation at the nitrogen atom is followed rapidly by monodeprotonation of the benzylic methylene function, further oxidation and decomposition.

In the case of laudanosine(206)[164,6,166] the cyclic voltammogram of the substrate displays a large peak at +1.1V (measured with respect to Ag- 0.1M $AgNO_3$ in acetonitrile) which was shown by comparison with other dimethoxyated compounds to correspond to the oxidation of a dimethoxylated aryl ring. A smaller peak at +0.55V was similarly shown to correspond to the oxidation of a tertiary amine and it was found that the preparative oxidation could be performed at either +0.55V or at +1.1V giving in either case the same morphandienone(207). While at +1.1V the oxidation was assumed to occur by standard processes the low potential reaction was explained through anchimeric assistance by the nitrogen atom by means of homoconjugation (Sceme XIII). The first step was envisaged as a one electron loss to form the radical cation (214), which is stabilised by homoconjugation, followed by further oxidation to form the coupled dication(215). As this is also stabilised by homoconjugation the coupling process is facile and the loss of a proton to form the cation(216) followed by water to produce the intermediate(217) leads by the loss of formaldehyde to the product(207).

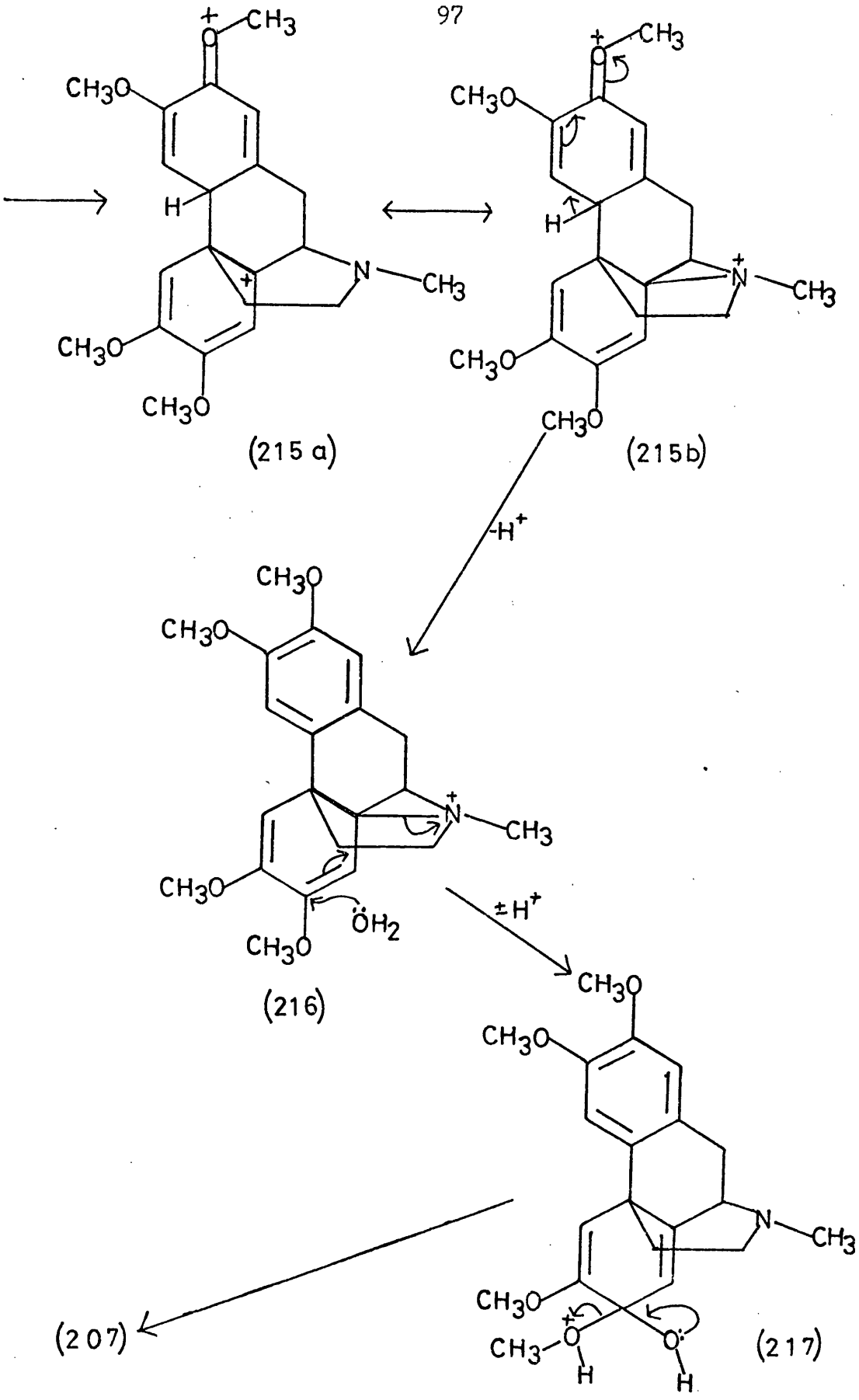
Application of the same arguments to the 4-benzyl-

analogue(213) leads to a possible explanation for the failure of its electrochemical oxidation (Scheme XIV). A one electron oxidation leads to a radical cation(218) stabilised by homoconjugation. Cyclisation would lead to a dication which is not so stabilised (219) and hence this change is less favoured than in the previous case. Formation of a five-membered ring would allow this stabilisation but this would impose a greater strain on the system[169].

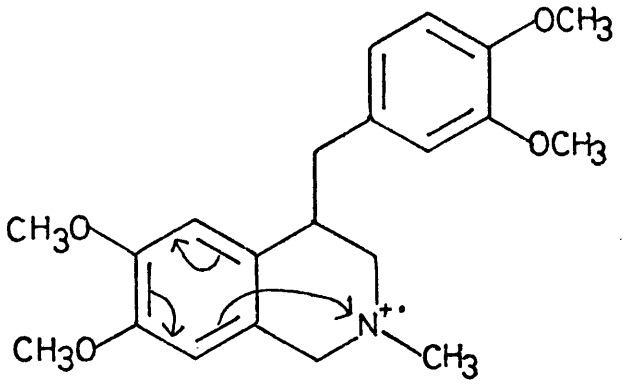
By changing the electrolyte to dichloromethane and trifluoroacetic acid containing tetra-n-butylammonium tetrafluoroborate it was expected that oxidation of the nitrogen atom would cease to be a problem as the substrate will now exist principally as the isoquinonium salt(220). Indeed the cyclic voltammogram (fig. 4 p.171) now shows the first oxidation peak as a broad band centred at +1.4V followed by a further electron loss at +1.9V. A preparative electrolysis at the lower potential did not however lead to aryl-aryl coupling but gave instead the 3,4-dihydroisoquinolinium salt (221), whereas oxidation at the higher value afforded the benzylidene derivative(222). A rationalisation of the formation of these two products is given in Scheme XV. They are however accompanied by much resinous material and it is probable that other compounds produced, for example, by intermolecular coupling reactions of the 3,4- dimethoxybenzyl ring system, are destroyed by the severity of the electrolysis conditions. It seems, therefore that, in order to achieve the desired intramolecular union between the two methoxylated rings, their oxidation potentials should be very closely


-e
CH3O
CH3O
N+·
CH3
OCH3
OCH3
(214a)
CH3O
CH3O
N+
CH3
OCH3
OCH3
(214b)
CH3O
CH3O
+·
N
CH3
-e
OCH3
OCH3
(214c)

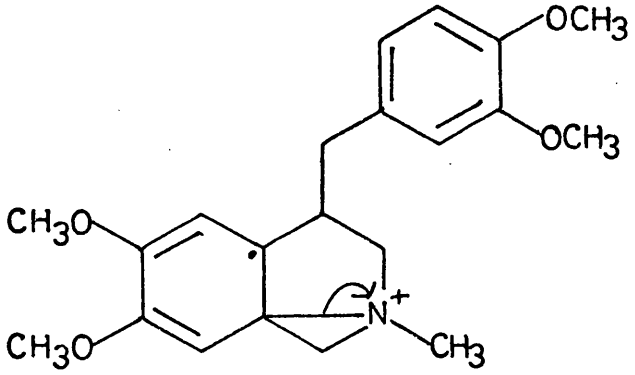
Scheme XIII



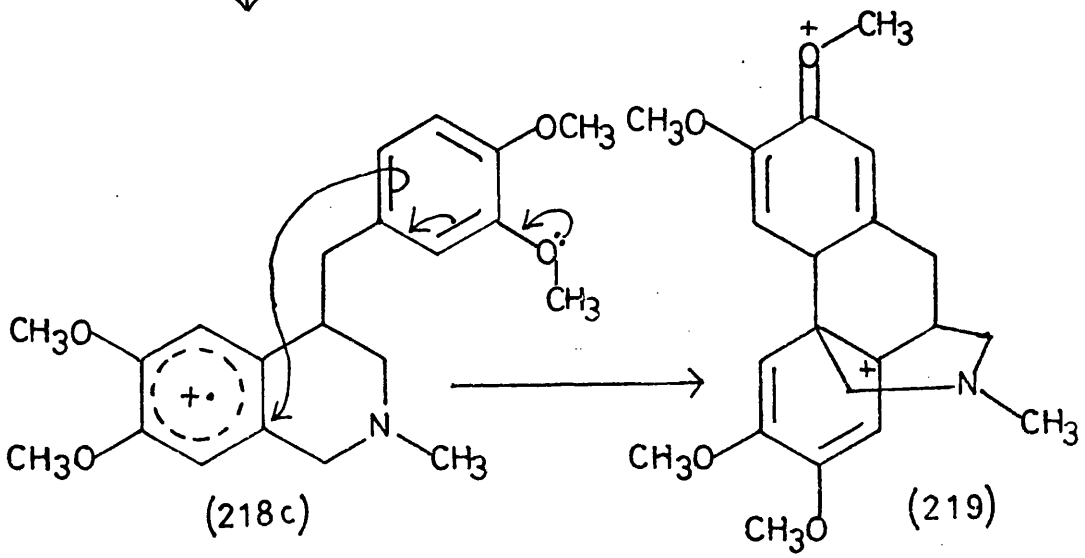
Scheme XIII continued



(218a)

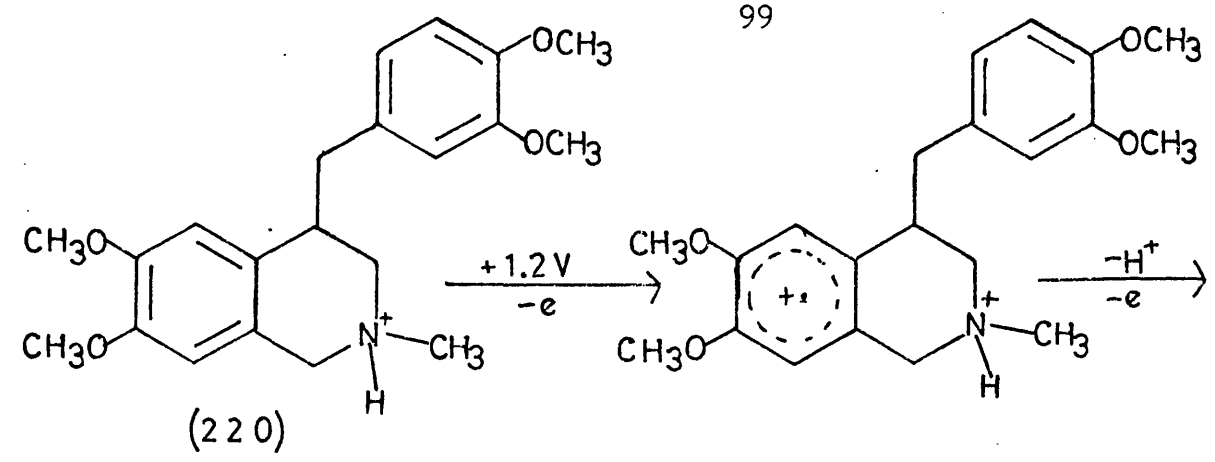


(218b)

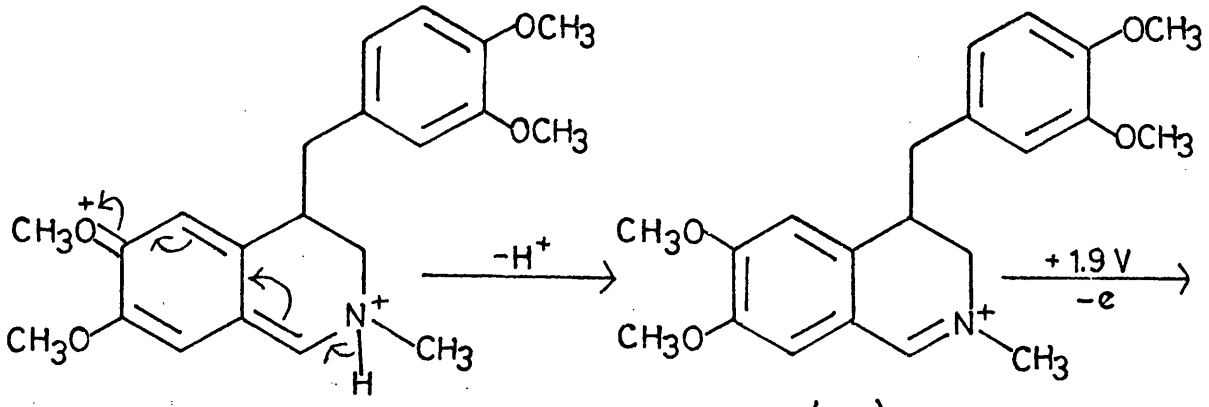


(218c) (219)

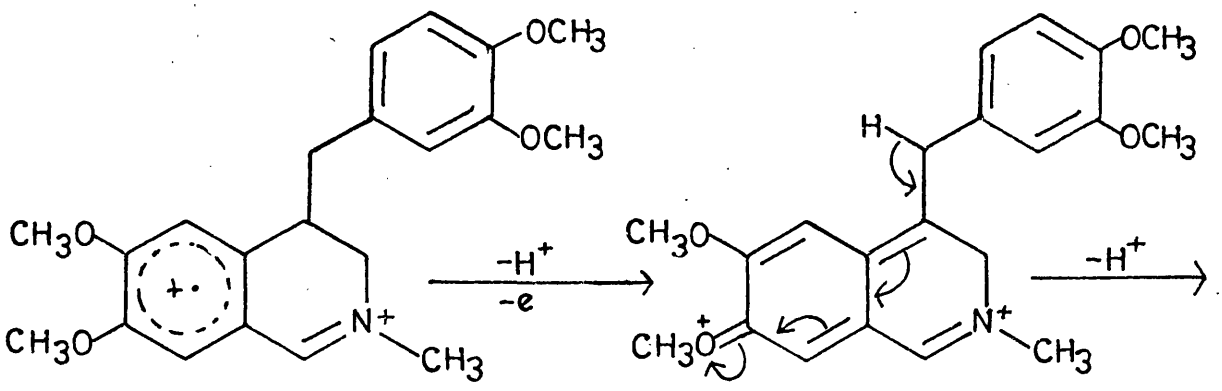
Scheme XIV

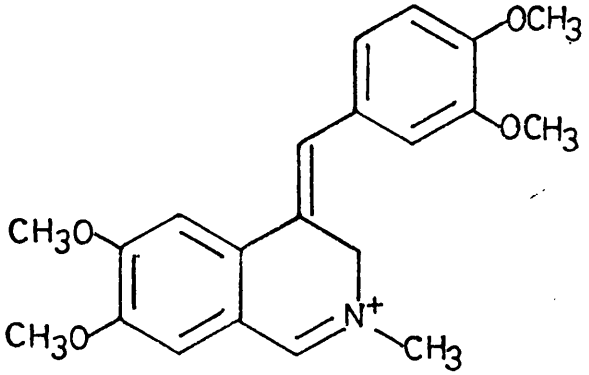


(220)



(221)





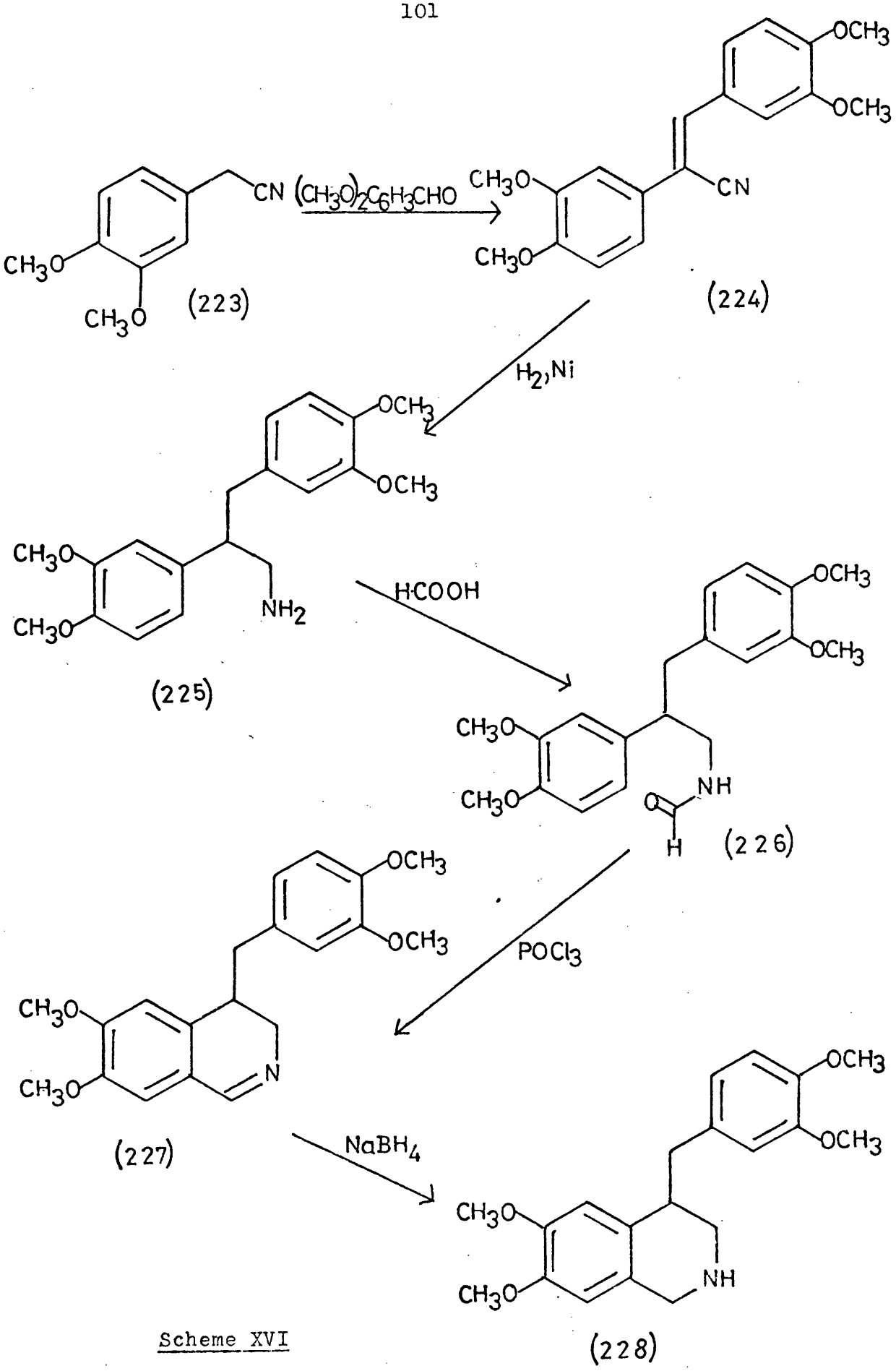
(222)

Scheme XV

similar. In the isochromanone(4a), for example, both aromatic rings lose an electron to a platinum anode at 1.1V, but the effect of protonation on the nitrogen atom of the tetrahydroisoquinoline(213) is to raise the oxidation potential of the benzenoid ring fused to the heterocycle to 1.4V and thus facilitate 3,4-dihydroisoquinoline salt formation. The presence of a basic nitrogen atom is equally undesirable and it was thus decided to study the electrochemistry of an appropriate N-acyl-1,2,3,4-terahydroisoquinoline.

It seemed that these compounds would be best prepared by the acylation of 1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline(228) and Bichler-Napieralski synthesis was selected as the easiest method of obtaining this compound (see introduction p.39)(Scheme XV). [E]-α-(3,4-Dimethoxyphenyl)-3,4-dimethoxycinnamonitrile(224) was prepared by the condensation of 3,4-dimethoxyphenylacetonitrile(223) and 3,4-dimethoxybenzaldehyde and was reduced using Raney nickel to form 2,3-bis-(3,4-dimethoxyphenyl)propylamine(225). This compound when heated with excess formic acid to a temperature of 200°C formed N-(2,3-bis-(3,4-dimethoxyphenyl)propyl)formamide(226) in good yield.

Formamides, similar to compound(226) have in the past been cyclised by heating with phosphoryl chloride in toluene[93] and it was hoped that this method would also prove effective in this case. In practice, however, a complex mixture of products was produced and rather than attempt a separation which would at best give only a poor yield of the 3,4-dihydroisoquinoline(227) it was decided to attempt a synthesis of

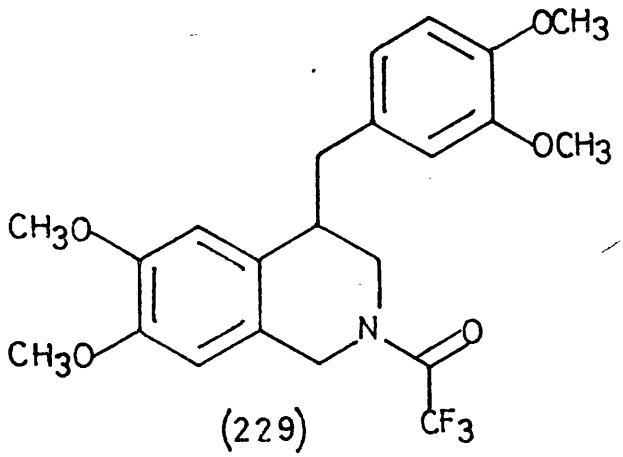

OCH3
OCH3
CN
(CH3O)2C6H3CHO
CH3O
CN
CH3O
CH3O
(223)
(224)
H2,Ni
OCH3
OCH3
CH3O
CH3O
NH2
(225)
HCOOH
OCH3
OCH3
CH3O
CH3O
NH
O
H
(226)
POCl3
OCH3
OCH3
CH3O
CH3O
N
(227)
NaBH4
OCH3
OCH3
CH3O
CH3O
NH
(228)

Scheme XVI

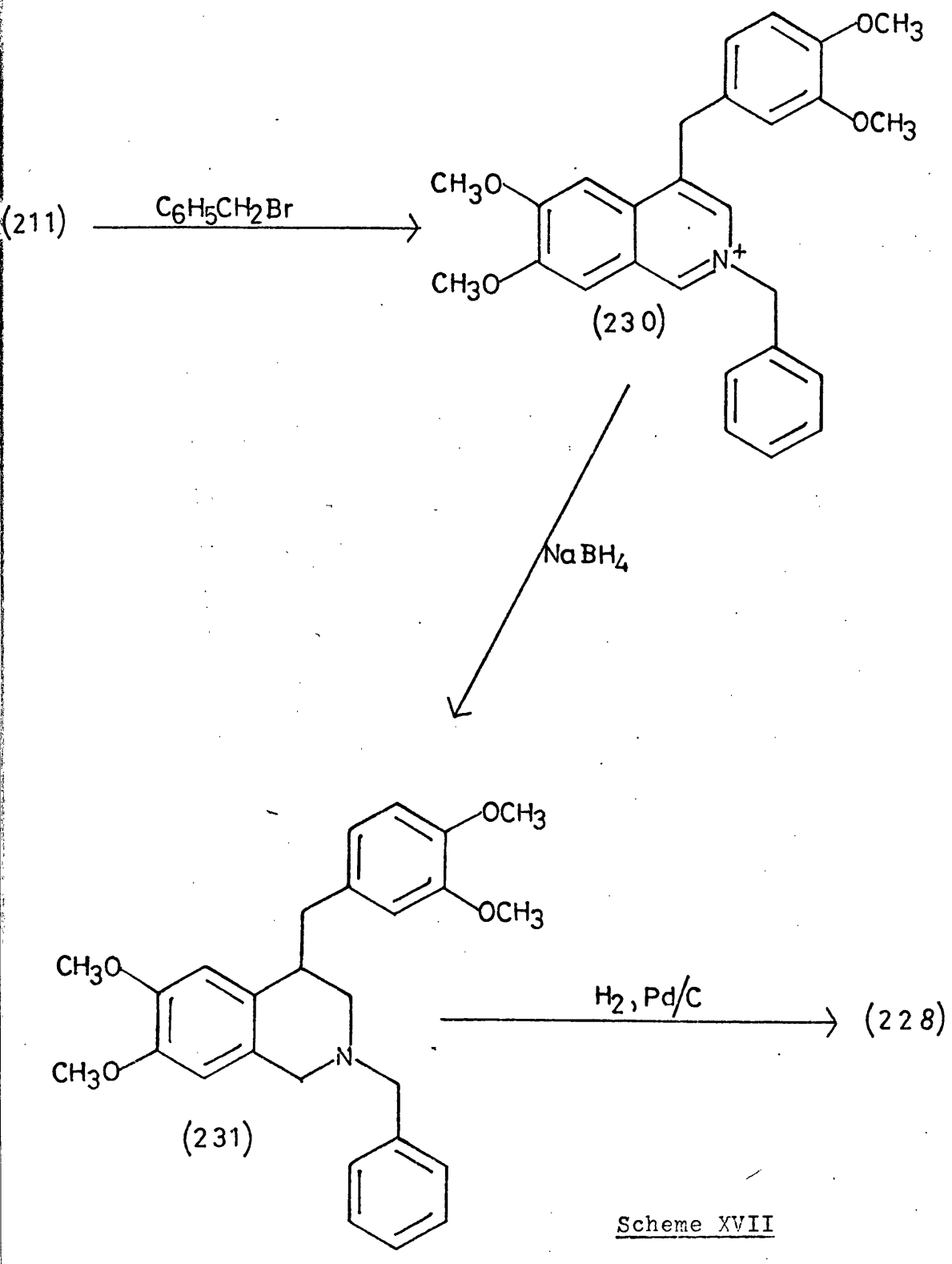
the tetrahydroisoquinoline by another route.

Direct catalytic reduction of the fully aromatic isoquinoline(211) failed under all the conditions tried. The most severe being at a hydrogen pressure of 20 atm. and a temperature of 100°C using 2M hydrochloric acid as the solvent and platinum oxide as the catalyst. This failure caused us to consider hydrogenolysis of the N-benzyl-tetrahydroisoquinoline(231). This was prepared by sodium borohydride reduction of the benzyl bromide salt(230) which was in turn prepared by treating the isoquinoline(211) with benzyl bromide. Hydrogenolysis of the N-benzyl compound(230) failed to take place under a variety of conditions but was eventually performed successfully upon the hydrochloride salt using palladium on charcoal as the catalyst. This then gave the tetrahydroisoquinoline(228) in excellent yield.

The acyl derivative chosen as a substrate for electrochemical investigation was the trifluoroacetyl compound(229). This was selected in preference to an acetyl substituent as N-acetyl groups are liable to be lost as ketene during electrolysis[165].



(229)


(211)
$C_6H_5CH_2Br$
CH_3O
CH_3O
OCH_3
OCH_3
N^+
(230)
$NaBH_4$
CH_3O
CH_3O
OCH_3
OCH_3
N
(231)
H_2, Pd/C
(228)

Scheme XVII

Trifluoroacetylation was achieved in good yield by treating the isoquinoline(228) with trifluoroacetic anhydride in the presence of potassium carbonate. The signals in the region δ4.1- 4.9 of the ^{1}H n.m.r. spectrum of this product showed considerable simplification on raising the temperature from 35°C to 110°C (p.168 to 169) thus presenting evidence for restricted rotation of the trifluoroacetyl group about the C-N bond.

The cyclic voltammogram of 2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline (229) (fig. 5 p.171) shows an anodic peak due to a non-reversible oxidation at 0.97V and at potentials up to 1.3V there is no evidence of the oxidation of a product. A preparative experiment using carbon felt electrodes was conducted but it was not possible to monitor the reaction by thin layer chromatography because of "steaking" of the spots during development. The reaction was therefore allowed to proceed to completion as judged by a drop in the current flowing from 500 mA to 10 mA. Electrolysis proceeded very smoothly as judged from the current and electrode filming was not encountered. Unfortunately no tangible product could be isolated from this reaction, only a gumy tar. Even so this showed a broad carbonyl band (1660 cm^{-1}) in the infra-red spectrum not incompatible with the stretching frequencies expected for the trifuoroacetyl group and/or the carbonyl of a dienone .

These experiments were conducted at the laboratories of Glaxo whilst the author was on placement and clearly they

need to be repeated back at Bath where it will be possible to more closely control the anode potential. It seems most likely that over oxidation is occuring in this electrolysis but the cyclic voltammetric evidence shows that under more controlled conditions i.e. an anode potential of less than +1.3V this effect may be repressed and an isomorphinandienone should be produced.

EXPERIMENTAL

A Perkin Elmer 402 spectrometer was used to record u.v. spectra of solutions in analytical reagent grade methanol and a Perkin Elmer 237 machine was used to record i.r. spectra. The ^{1}H n.m.r. spectra were recorded at 100 MHz on a Jeol PS 100 spectrometer using tetramethylsilane as an internal standard and mass spectroscopic data were obtained using a AEI MS 12 instrument.

All electrolyses were conducted with an H-type cell with an anolyte capacity of $150cm^3$. Unless stated otherwise, acetonitrile (distilled from phosphorus pentoxide under dry nitrogen) was used as the solvent and anhydrous sodium perchlorate (dried under reduced pressure ar $125^{o}C$ for twenty-four hours) formed the supporting electrolyte. Graphite felt was used for both electrodes. The electrode potential was monitored by a calomel electrode connected to the cell *via* an agar/potassium chloride conducting bridge and the current was provided by a Farnell stabilized power supply.

A typical preparative experiment was conducted by dissolving ~1g of substrate in the anolyte and the external supply voltage increased until either a predetermined electrode potential was reached, or a practical current flow (15-60mA) was obtained. When the appropriate amount of current had been consumed the anolyte was poured into water ($\sim 600cm^3$) and the solution extracted with dichloromethane. The combined, dried, organic extracts were evaporated to give the crude anodic product, after which normal separation procedures

were followed.

All cyclic voltammograms were recorded using a 'home-built' three electrode polarograph constucted by Dr. J.A. Wyatt[7] . Voltammograms were displayed on either a Telequipment 261A oscilloscope or Hewlett Packard flat bed X-Y recorder (1 sec. pen response). Platinum wire or platinum bead microelectrodes were used as anodes for voltammetric measurements in a simple three electrode cell.

6,7-Dimethoxy-3-isochromanone(166)[156].

A solution of 3,4-dimethoxyphenylacetic acid (20g ; 0.1mol) in hot glacial acetic acid ($60cm^3$) was added to a mixture of concentrated hydrochloric acid ($20cm^3$) and aqueous formaldehyde solution (33% ; $20cm^3$) and heated on a steam bath for one hour. Water ($200cm^3$) was then added and the mixture extracted with chloroform ($3x40cm^3$). The extracts were combined and washed with saturated sodium bicarbonate solution until carbon dioxide ceased to be evolved. The solution was then dried over magnesium sulphate and evaporated under reduced pressure to yield a yellow solid which was recrystallised from ethanol ($70cm^3$) to produce colourless needles (13.4g ; 64%), m.p. 107-108°C, lit., 108-109.5°C[156]. All spectral properties agreed with those previously reported[7].

6,7-Dimethoxy-4-(3,4-dimethoxybenzylidene)-3-isochromanone(168).

6,7-Dimethoxy-3-isochromanone (20.8g; 0.1mol), 3,4-

dimethoxybenzaldehyde (16.6g ; 0.1mol) and piperidene (1.0g) were heated, under an atmosphere of nitrogen and with stirring, to a temperature of 130°C. After two hours heating was stopped and, when the temperature of the mixture had dropped to 100°C, glacial acetic acid ($40cm^3$) was added and the mixture left to cool to room temperature . The resulting yellow precipitate was filtered off and washed with ethanol ($60cm^3$) and diethyl ether ($60cm^3$). The product was normally used without further purification, but successive recrystallisation from ethanol produced pure E-4-(3,4-dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone. Upon standing the combined mixture of mother liquor and washings produced a crop of yellow platelets which was found to be a mixture of E and Z-isomers. Further crops were found to be progressively richer in the Z-isomer until eventually a mixture of yellow platelets and fine orange needles was formed. The orange needles could be separated by repeated decantation of the less dense yellow platelets and were recrystallised from ethanol to produce yellow platelets of pure Z-4-(3,4-dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone.

overall yield; 29.2g, 82%

yield of pure E-isomer; 15.7g, 44%

yield of pure Z-isomer; 5.2g , 14%

m.p. E- 176-177°C, Z- 146-147°C. lit., 176-177°C[156]

^1H n.m.r. $\delta(CDCl_3)$, E :- 7.71(s, 1H, f (see p. 67)), 7.15 (dd, 1H, b, J= 8, $2H_3$), 7.11,7.01(2s, 2H, c and e), 6.82(d, 1H, a, J= $8H_3$), 6.74(s, 1H, d), 5.29(s, 2H,

$ArC\underline{H}_2$), 3.91, 3.75, 3.58(3s, 12H, $4xOC\underline{H}_3$)p.151.

Z:- 7.78(d, 1H, c, J= $2H_3$), 7.31(dd, 1H, b, J= 2, $8H_3$), 7.08, 7.03(2s, 2H, e and f), 6.85(d, 1H, a, J= $8H_3$, 6.70(s, 1H, d), 5.20(s, 2H, $ArC\underline{H}_2$), 3.97, 3.91(2s, 12H, $4xOC\underline{H}_3$)p.152.

i.r. (0.5% $CHBr_3$) $\bar{\nu}_{max}$, cm^{-1}; E:- 2740($ArOCH_3$), 1718(CO), 1021, 1046(OCH_3).p.151.Z:- 2740($ArOCH_3$), 1722(CO), 1023, 1033(OCH_3)p.156.

u.v. λ_{max}, nm(ξ, $1mol^{-1}cm^{-1}$); E:- 246(16,900), 362(16,900). Z:- 246(16,600), 362(21,600).

Analysis: found (E) C, 67.6; H, 5.5. (Z) C, 67.7; H, 5.5. $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.7%.

h.p.l.c. Portions of the reaction mixture were removed after 10,30,120 minutes. A further sample after 120 minutes was heated to 160-170°C for two hours. The crude mixtures were treated with glacial acetic acid, dissolved in dichloromethane and, these solutions, washed with sodium bicarbonate solution, water, dried over magnesium sulphate and evaporated under reduced pressure. The four crude products produced were analysed by ^1H n.m.r. using the methoxy peaks to give crude isomer ratios but h.p.l.c. gave these ratios with greater accuracy.

Column: 20cm Particil 5, mobile phase, hexane:ethyl acetate: isopropanol(100:25:5), flow rate $1.8cm^3mm^{-1}$ detection u.v. at 356nm retention times E-isomer 6.1 min, Z-isomer 5.3 min.

SAMPLE	RATIO E:Z		
	1.	2.	MEAN
"Pure E-isomer	84.73:15.27	83.64:14.36	84.18:14.81
"Pure Z-isomer	13.48:86.52	12.89:87.12	13.18:86.82
Reaction mixture after 10min	70.00:30.00	70.40:29.60	70.20:29.80
Reaction mixture after 30min	65.15:34.85	65.07:34.93	65.11:34.89
Reaction mixture after 120min	67.86:32.14	66.75:33.25	67.30:32.70
Reaction mixture after 240min	55.58:44.42	55.51:44.49	55.54:44.46

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)-3-isochromanone(4a)[7].

6,7-Dimethoxy-4-(3,4-dimethoxybenzylidene)-3-isochromanone (8.9g;0.025mol) was dissolved in glacial acetic acid (350cm^3) and placed in a one litre glass hydrogenation vessel together with Adams catalyst (0.15g). The solution was hydrogenated at a temperature of 25-30^{o}C at a pressure of 4atm for eight hours. The mixture was then filtered and the solvent evaporated under reduced pressure to produce a clear oil. The oil was dissolved in hot ethanol (25cm^3) amd left to cool producing a white precipitate of 6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-3-isochromanone(8.5g;94%).

m.p. 107.5-108^{o}C, lit., 107-108^{o}C[156]

i.r. $\bar{\upsilon}_{max}$, cm^{-1}(nujol mull) 3600(enolic-O-H), 1720(γ-lactone

carbonyl), 1600,1580.

Other spectral properties agreed with those previously reported[7].

Ethyl 2-(2-bromomethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionate(170)[7].

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)-3-isochromanone (21.0g;0.007mol) was added to a stirred solution of hydrogen bromide (10.0g;0.14mol) in anhydrous ethanol (100cm^3). The mixture was left stirring for 24 hours during which time the solid slowly dissoved to give a pale orange solution. The solution was evaporated at 25°C under reduced pressure to yield a pale yellow oil which on standing for some weeks formed pale yellow needles.(2.32g;71%),

m.p. 82-84°C, lit., 84°C[7]

The whole of the above procedure was carried out so as to exclude , as far as possible, air, moisture and light. The product being unstable to all of these especially the latter. The product was normally used as an oil immediately after preparation because of its instability and the time taken for crystallisation when this was done a yield of 90% from the isochromanone was assumed.

All spectral properties agreed with those previously reported[7].

5-Carbethoxy-2,3,8,9-tetramethoxy-dibenzo[b,f]cycloheptane (171).

A crude sample of ethyl 2-(2-bromomethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionate (2.5g;0.05mol)

was dissolved in a mixture of dry toluene ($70cm^3$) and anhydrous ethanol ($20cm^3$) this solution was added dropwise over approximately one hour to a stirred suspension of anhydrous potassium carbonate (15.0g) in anhydrous ethanol ($50cm^3$). The mixture was allowed to stir overnight and was then filtered and the solvent removed by evaporation under reduced pressure to yield a pale yellow oil. This oil was dissolved in chloroform ($50cm^3$), washed with water (2x $50cm^3$), dried using sodium sulphate and the solvent removed by evaporation under reduced pressure to produce a pale yellow solid. The solid was dissolved in ethanol ($30cm^3$) boiled with activated charcoal, filtered and left to cool whereupon colourless plates were formed (1.4g;72%),

m.p. 108-110°C

^{1}H n.m.r. $\delta(CDCl_3)$; 6.80-6.72(m, 3H, 3x ArH), 6.65(s,1H, ArH, (6-position)), 4.14(q,2H,OCH_2CH_3), 4.04(s,2H, $ArCH_2Ar$), 3.86,3184,3.81, 3.78(4s, 3H each, 4x OCH_3), 3.80-3.60(m,1H, $ArCH_2CHAr$), 3.26, 3.28 (m, 2H, $ArCH_2CHAr$), 1.22(t, 3H, J= $7H_3$, CH_2CH_3).

i.r.(nujol mull) $\bar{\upsilon}_{max}$, cm^{-1}, 1715(CO),1610, 1515, 1380.

Mass Spectrum m/e (rel. abundance,%),385(55)M-1, 312(100), 165(97), 152(85), 151(42)

metastables, 252.8(385-312)

Analysis; found C, 68.3;H, 6.7. $C_{22}H_{26}O_6$ requires: C, 68.4; H, 6.8%.

N-Methyl-2-(2-hydoxymethyl-4,5-dimthoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide(172)[156].

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)-3-isochromanone (6.0g;0.017mol) was heated under reflux conditions for one hour in an ethanolic solution of methylamine ($50cm^3$;33%). The excess methylamine and the ethanol were then removed by by evaporation under reduced pressure and the resulting colourless oil was dissolved in hot ethanol ($20cm^3$) and , upon cooling, the product was obtained as white plates (4.05g;61%).

m.p. 146-147°C, lit., 147-148°C[156]

All spectra were identical with those previously reported[156].

2,3,8,9-Tetramethoxy-5-(N-methylformamido)-dibenzo[b,f] cycloheptane(173).

Ethylpolyphosphoric ester ($5.0cm^3$) was added to a solution of N-methyl-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide (1.0g;0.0026mol) in chloroform ($25cm^3$). After thorough mixing the solvent was removed by evaporation under reduced pressure and the resulting oil was heated, under an atmosphere of dry nitrogen, to a temperature of 140°C which was maintained for 15 minutes. The mixture was then allowed to cool and was poured into water ($100cm^3$). The mixture was extracted with chloroform (3x $20cm^3$) and the combined organic extracts were washed with saturated sodium chloride solution ($20cm^3$) water ($20cm^3$), boiled with activated charcoal, filtered and dried over sodium sulphate.

The solvent was evaporated under reduced pressure to yield a white solid which was recrystallised from ethanol($30cm^3$) to produce white needles (0.71g;71%).

m.p. 199-199.5°C

^1H n.m.r. $\delta(CDCl_3)$; 6.76-6.58(m, 3H, 3(ArH)), 6.51(s, 1H, ArH(5-position)), 4.96(q, 1H, NH), 4.00(t, 1H, ArCHCO, J= $5H_3$), 3.96(q(AB), 2H, $ArCH_2Ar$), 3.88, 3.84, 3.80, 3.75(4s, 4x 3H, 4x OCH_3), 3.20-3.60 (m, 2H, $ArCHCH_2Ar$), 2.54(d, 3H, NCH_3, J= $5H_2$) p.157.

i.r. (nujol mull) $\bar{\upsilon}_{max}$, cm^{-1}, 3300(NH), 1640(2° amide carbonyl), 1610, 1560.p.158.

u.v. λ_{max}, nm(ξ,$1mol^{-1}cm^{-1}$);237(5,910), 287(5,230).

Mass Spectrum; m/e (rel. abundance,%), 371(49)M, 313(100), 298(9), 282(15).

metastables; 264.1(371-313), 254.1(313-298).

Analysis; found: C, 67.9; H, 6.8; N, 3.8. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.8%.

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)-3-isochromanone(4a); attempted preparation of 2-(3,4-dimethoxyphenyl)-1-(3,4-dimethoxy-6-methyltosylphenyl)-N-methyl propionamide(174).

1-(2-Hydroxymethyl-4,5-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)-N-methyl propionamide (1.0g;0.0026mol) was dissolved in pyridine ($100cm^3$) and tosyl chloride (0.65; 0.003mol) was added. The mixture was then heated under reflux conditions for eight hours, after which time the solvent was removed by evaporation under reduced pressure and the

resulting yellow oil dissolved in dichloromethane ($50cm^3$), washed with brine ($3x\ 50cm^3$), water ($50cm^3$) and dried over magnesium sulphate. The solvent was then removed by evaporation under reduced pressure to yield a pale yellow oil which was dissolved in hot ethanol ($20cm^3$). Upon cooling 6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-3-isochromanone was obtained as a white solid (0.73g;68%),
m.p. 106.5-107.5°C,lit.,107-108°C[156].

All spectral properties agree with those previously reported[7].

Silver tosylate[157].

p-Toluenesulphonic acid (19.06;0.11mol)was dissolved in acetonitrile ($250cm^3$) and to the solution was added commercial silver oxide (11.65g). The mixture was then stirred at room temperature for two hours. After this time unreacted silver oxide was removed by filtration and the solvent removed from the filtrate by evaporation under reduced pressure to yield the product as a white powder (30.7g;89%). This was used without further purification,
m.p. 325°C
i.r. (nujol mull) $\bar{\upsilon}_{max}$, cm^{-1}, strong bands in 1200-1100 region.

1-(2-Chloromethyl-4,5-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)-N-methyl propionamide

1-(2-Hydroxymethyl-4,5-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)-N-methyl propionamide (1.0g;0.0026mol) was dissolved

in dry tetrahydrofuran ($100cm^3$). To this solution was added thionyl chloride (5.0g) which had been freshly distilled from quinoline and the mixture heated to boiling point over a period of twenty minutes. After this time excess thionyl chloride and the solvent were removed by evaporation under reduced pressure to yield a pale yellow gum (0.97g;92%) which was used without further purification.

i.r.(film) $\bar{\upsilon}_{max}$, cm^{-1}, no OH, 1665(CO).

2,3,8,9-Tetramethoxy-5-(N-methylformamido)-dibenzo[b,f]cycloheptane(173); attempted preparation of 2-(3,4-dimethoxyphenyl)-1-(3,4-dimethoxy-6-methyltosylphenyl)-N-methyl propionamide(174).

Crude 1-(2-chloromethyl-4,5-dimethoxyphenyl-2-(3,4-dimethoxyphenyl)-N-methyl propionamide (1.3g;0.0032mol) was dissolved in acetonitrile ($50cm^3$) and added to a solution of silver tosylate (0.9g;0.0032mol) in acetonitrile ($50cm^3$). An immediate white precipitate of silver chloride was observed. After allowing the reaction mixture to stand overnight this precipitate was removed by filtration and the solvent was then removed from the filtrate. The residual solid was dissolved in a mixture of dichloromethane ($30cm^3$) and diethyl ether ($70cm^3$). After standing a further fine precipitate of silver chloride was observed which again was removed by filtration and then the solvent removed from the filtrate by evaporation under reduced pressure. Thus yielding a pale yellow gum which was dissolved in hot ethanol ($10cm^3$). On cooling the product was formed as a white powder(0.68g;57%),

m.p. 197-198°C

All spectral data agree with those previously described (page114).

N,N-Dimethyl-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl) propionamide(175)[158].

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)-3-isochromanone (6.0g;0.017mol) was heated under reflux conditions for five hours in an ethanolic solution of dimethylamine (33%,50cm^3). The excess dimethylamine and the ethanol were then removed by evaporation under reduced pressure and the resulting pale yellow oil was dissolved in hot ethanol, boiled with activated charcoal, filtered and upon cooling the product appeared as a white solid (4.85g;71%).

m.p. 134-135°C,lit., 144°C[158].

^{1}H n.m.r. $\delta(CDCl_3)$; 7.06, 6.78(2s, 2x 1H, 2x ArH (hydroxymethyl substiutted ring)), 6.7-6.48(m, 3H, 3x ArH), 4.42(A-Bq, 2H, CH_2OH), 4.24(t, 1H, CHCON, J= 7H_3), 3.87, 3.84, 3.80, 3.71(4s, 4x 3H, 4x OCH_3), 3.02-2.68(m, 7H, 2x NCH_3, OH(reduced to 6H upon deuteriation)).

i.r. (nujol mull) $\bar{\nu}_{max}$, cm^{-1}; 3380(H-bonded O-H), 1620(tertiary amide carbonyl), 1600, 1580.

u.v. λ_{max}, nm (ξ, $1mol^{-1}cm^{-1}$); 242(8,460), 281(5,860).

Mass Spectrum: m/e (rel. abundance, %); 403(37)M, 385(16), 313(99), 179(98), 151(100).

metastables; 3678(403-385), 245.5(385-313), 243.1(403-313), 127.4(179-151).

Analysis; found: C, 66.0; H, 6.9; N, 3.7. $C_{22}H_{29}NO_6$ requires C, 65.5; H, 7.2; N, 3.5%.

N,N-Dimethyl-2-(2-formyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl) propionamide(176)[158].

N,N-Dimethyl-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl) propionamide (3.0g;0.007mol) dissolved in chloroform (100cm^3) was shaken with activated manganese dioxide (25.0g)[167] for 48 hours. The mixture was then filtered and the chloroform removed by evaporation under reduced pressure to yield a pale yellow oil. The oil was dissolved in hot ethanol (25cm^3) and upon cooling, the product was obtained as a white solid (2.1g;71%).

m.p. 104-105°C, lit., 144°C[158].

^{1}H n.m.r. $\delta(CDCl_3)$, 9.83(s, 1H, ArC<u>H</u>O), 7.23, 7.17(2s, 2x 1H, 2x Ar<u>H</u> (formyl substituted ring)), 6.75-6.65(m, 3H, 3x Ar<u>H</u>), 5.40(t, 1H, C<u>H</u>CON, <u>J</u>= 7H_2), 3.96, 3.92, 3.82, 3.80(4s, 4x 3H, 4x OC<u>H</u>$_3$), 3.45, 3.22 (m, 2H, ArC<u>H</u>$_2$CH), 2.90,2.78(2s, 2x 3H, 2x NC<u>H</u>$_3$).

i.r. (nujol mull) $\bar{\upsilon}_{max}$, cm^{-1}; 1680(aryl aldehyde carbonyl), 1625(tertiary amide carbonyl), 1600, 1560.

u.v. λ_{max}, nm (ξ, $1mol^{-1}cm^{-1}$); 243(11,600), 283(9,960), 310(5,780).

Mass spectrum; m/e (rel. abundance,%); 401(0.8)M, 383(41), 311(6), 151(100).

metastables; 365.8(401-383), 252.5(383-311).

Analysis; found: C, 66.0; H, 6.6; N, 3.7. $C_{22}H_{27}NO_6$ requires C, 65.8; H, 6.8; N, 3.5%.

3-Hydroxy-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinolinium chloride(179)[158].

A solution of N,N-dimethyl-2-(2-formyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl) propionamide (3.0g,0.007mol) in ethanolic methylamine ($50cm^3$;33%) was heated under reflux conditions for three hours. Ethanol and excess methylamine were then removed by evaporation under reduced pressure to yield the imine as a green gum. The gum was dissolved in hydrochloric acid ($80cm^3$;6M) at a temperature of approximately 60^oC. The product was obtained as white needles upon cooling (2.3g;81%). The product was found to be sensitive to aerial oxidation and to light.

m.p. 210-212°C

^1H n.m.r. $\delta((CD_3)_2SO)$; 8.80(s, 1H, ArH, 1-position), 7.2-6.7 (m, 5H, 5x ArH), 4.3(br.s, 2H, $ArCH_2$), 3.9-3.7 (5x s, 15H, 5x OCH_3)

i.r. (nujol mull) $\bar{\upsilon}_{max}$, cm^{-1}; 3480(OH), 1645($C=N^+$), 1608.

u.v. λ_{max}, nm (ξ, $1mol^{-1}cm^{-1}$), 227(21,700), 254.5(55,100), 307.5(4,150), 318.5(4,500), 404(4,550).

Mass spectrum; m/e (rel. abundance,%), 369(100)M, 354(95), 338(44), 298(32), 151(100).

metastables; 339.6(369-354), 309.6(369-338), 250.9(354-298).

Analysis; found: C, 62.3; H, 6.1; N, 3.1% $C_{21}H_{24}ClNO_5$ requires C,62.1; H, 5.9; N, 3.5%.

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)-2-methyl-3(2H)-isoquinolinone(180).

3-Hydroxy-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methyl-isoquinolinium chloride (3.1g;0.0076mol) was dissolved in dichloromethane (50cm^3) and extracted with saturated sodium bicarbonate solution until no further evolution of carbon dioxide was detected. The solution was then washed with water (50cm^3), dried over magnesium sulphate and evaporated under reduced pressure to yield a pale yellow solid which was recrystallised from ethanol (10cm^3) to yield the product as a white solid (2.6g;92%).

m.p. 165-168°C.

^{1}H n.m.r. $\delta(CDCl_3)$, 7.83(s,1H, ArH, 1-position), 6.96(d, 1H, J=2H$_3$, 2-position 4-benzyl substituent), 6.85-6.70(m, 3H, 5- and 6-positions 4-benzyl substituent + either 5- and 8-position heterocyclic ring), 6.57 (s, 1H, ArH 8- or 5-position), 4.20(s, 2H, $ArCH_2$), 3.87-3.71(m, 15H, 4x OCH_3 + NCH_3). p.159.

i.r. (0.5% $CHBr_3$) $\bar{\nu}_{max}$, cm^{-1}; 1650(CO), 1635, 1255, 1040. p.160.

Analysis; found: C, 68.1; 6.0; N, 4.1. $C_{21}H_{23}NO_5$ requires, C, 68.3; H, 6.2; N, 3.8%.

N-Amino-1-(2-hydroxymethyl-4,5-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl) propionamide(181).

Hydrazine hydrate (0.25g;0.005mol) was added to a solution of 6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-3-isochromanone (1.5g;0.0042mol) in ethanol (50cm^3) and the mixture heated under reflux conditions for six hours. Half the solvent was left

overnight whereupon a white precipitate was produced which was recrystallised from ethanol ($15cm^3$) to produce a white solid (1.35g;82%).

m.p. 159-160°C.

^1H n.m.r. $\delta(CDCl_3)$; 8.92(s, 1H, OH, removed by deuteriation) 7.63(s, 1H, ArH), 6.88(s, 1H, ArH), 6.82-6.60 (m, 3H, 3x ArH) benzyl substituent), 5.08(s, 1H, $NHNH_2$, removed by deuteriation), 4.44(s, 2H, CH_2OH), 4.4-3.8(m, 2H, $NHNH_2$, removed by deuteriation, 3.70(s, 3H, OCH_3), 3.95-3.5(m, 1H, $ArCH_2CH$), 2,96 (AB part of ABX system, 2H, $ArCH_2CH$, $J_{AX}= 7H_3$ $J_{AB}= 19H_3$)

i.r. (nujol mull) $\bar{\nu}_{max}$, cm^{-1}; 3330, 3230-3070 broad band, 1690, 1640, 1600, 1510.

u.v. λ_{max}, nm (ξ, $1mol^{-1}cm^{-1}$); 238(10,500), 281(5,460).

Mass spectrum; m/e (rel. abundance,%); 390(10)M, 372(10), 313(23), 151(100).

metastables; 354.8(390-372), 263.4(372-313).

Analysis; found: C, 61.4; H, 6.7; N, 7.3. $C_{20}H_{26}N_2O_6$ requires C, 61.5; H, 6.7; N, 7.2%.

5-(N-amidoformamido)-2,3,8,9-tetramethoxy-dibenzo[b,f]cyclo-heptane(183).

N-amino-1-(2-hydroxymethyl-4,5-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl) propionamide (3.4g;0.0087mol) was heated under reflux conditions with 2M hydrochloric acid ($100cm^3$) for half an hour. The solution was then rendered basic to litmus by the addition of 2M sodium hydroxide solution

($100cm^3$) and the mixture was extracted with dichloromethane ($3x\ 30cm^3$). The combined organic extracts were washed with saturated sodium chloride solution ($30cm^3$), water ($30cm^3$) dried over magnesium sulphate and evaporated under reduced pressure to yield a pale yellow oil.This oil was dissolved in hot ethanol ($25cm^3$) and the product was obtained as a white solid on cooling (2.1g;65%).

m.p. 210-211°C.

^{1}H n.m.r. $\delta(CDCl_3)$, 6.78, 6.76(2s, 3H, 3x ArH), 6.57(s, 1H, ArH), 6.39(br.s, 1H, removed by deuteriation, $NHNH_2$), 4.3-3.5(m, 3H, $ArCH_2Ar$, $ArCH_2CH$), 3.93, 3.90, 3.87, 3.81(4s, 12H, 4x OCH_3), 3.70(br.s, 2H, $NHNH_2$, removed by deuteriation), 3.5-3.3(AB part of ABX, 2H, $ArCH_2CH$).

i.r. (sat. $CHBr_3$), $\bar{\nu}_{max}$, cm^{-1}; 3445(NH), 1660(CO), 2840, 1250, 1040 ($ArOCH_3$).

u.v. λ_{max}, nm (ξ, $1mol^{-1}cm^{-1}$); 234(9,400), 284(7,500).

Mass spectrum; m/e (rel. abundance,%); 372(43)M-1, 313(100), 282(20).

metastables; 263.4(372-313), 254.0(313-282).

Analysis; found: C, 62.3; H, 6.4; N, 6.9. $C_{20}H_{24}N_2O_5$ requires C, 62.0; H, 6.2; N, 7.2%.

5-Carboxy-2,3,8,9-tetramethoxy-dibenzo[b,f]cycloheptane(184).

N-Amino-1-(2-hydroxymethyl-4,5-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl) propionamide (4.1g;0.011mol) was heated under reflux conditions with 2M hydrochloric acid ($150cm^3$) for two hours. The solution was then added to water ($300cm^3$)

and the mixture extracted with dichloromethane (3x 50cm^3). The combined extracts were washed with water (50cm^3), dried over magnesium sulphate and evaporated under reduced pressure to a solid which was recrystallised from ethanol (30cm^3) to yield the product as a white powder (2.2g;56%).

m.p. 132-135°C.

^{1}H n.m.r. $\delta((CD_3)_2SO/CDCl_3$, 1:5), 11.5(br.s, 1H, COO<u>H</u>), 6.80 (s, 1H, Ar<u>H</u>), 6.75(s, 3H, 3x Ar<u>H</u>), 4.1(t, 1H, <u>J</u>= 9H$_3$, ArCH$_2$C<u>H</u>Ar), 3.75(4s + m, 14H, 4x OC<u>H</u>$_3$ + ArC<u>H</u>$_2$Ar), 3.6-2.9(8 lines, 2H, ArC<u>H</u>$_2$CHAr).

<u>i.r.</u> (nujol mull), $\bar{\upsilon}_{max}$, cm^{-1}; 35509(acid OH), 1650(CO), 1610.

<u>Mass spectrum</u>; <u>m/e</u> (rel. abundance,%), 358(100)M, 327(45), 313(100), 282(24).

<u>metastables</u>; 298.7(358-327), 254.1(313-282), 73.7(358-313).

<u>Analysis</u>; found: C, 66.9; H, 6.3. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%.

<u>Ethyl 2-bromomethyl-4,5-dimethoxyphenylacetate[7].</u>

To a solution of dry hydrogen bromide (20g) in anhydrous ethanol (300cm^3) was added 6,7-dimethoxy-3-isochromanone (10.0;0.048mol). The solution was stirred for 24 hours and the solvent evaporated at 20°C(3-5mm) to yield a colourless oil, which produced a white solid upon trituration with diethyl ether (14.0g;93%).

m.p. 54-57°C, lit., 55-57°C[7].

All spectral properties agreed with those previously reported[7].

In subsequent reactions this compound was used as an oil without further purification.

1,4-Dihydro-6,7-dimethoxy-2-methyl-3(2H)-isoquinolinone(187)[153].

A crude sample of ethyl 2-bromomethyl-4,5-dimethoxyphenylacetate (10.5g;0.035mol) was dissolved in a mixture of dry toluene ($50cm^3$) and anhydrous ethanol ($20cm^3$). The solution was then added dropwise, over a period of one hour, to a stirred suspension of anhydrous potassium carbonate (10g) in ethanolic methylamine (33%,$20cm^3$). The mixture was then left to stir overnight. After filtration and evaporation of the solvent and excess methylamine under reduced pressure, the residue was dissolved in dichloromethane ($50cm^3$). The solution was washed with water (2x $50cm^3$), dried over magnesium sulphate and evaporated under reduced pressure to yield a yellow oil which was dissolved in hot ethanol ($30cm^3$). Upon cooling pale yellow prisms were formed (4.3g;56%). A colourless product was obtained upon further recrystallisation from dry tetrahydrofuran.

m.p. 118-119°C, lit., 119.5-121.5°C[16].

All spectral properties agree with those previously reported[7].

Morpholinium perchlorate[160].

Morpholine (20.0g;0.23mol) was dissolved in dry diethyl ether ($150cm^3$) and perchloric acid ($40cm^3$ of a 1:1 mixture of A.R. perchloric acid in absolute ethanol) was slowly

added until the solution was just acid to congo red. Three drops of morpholine were then added and the mixture was left to stir at room temperature for two hours. The resulting precipitate was removed by filtration, recrystallised from 2-propanol ($150cm^3$) and dried at 50^oC under vacuum to yield the product as white needles (38.4g;89%).

m.p. 178-179°C.

^1H n.m.r. $\delta(D_2O)$; 3.92(t, 4H, J= $5H_3$, 2x OCH_2), 3.28(t, 4H, J= $5H_3$, 2x NCH_2).

i.r. (nujol mull) $\bar{\nu}_{max}$, cm^{-1}; 3200, 3150, 3075 (NH_2), 1110 (ClO_4^-).

N-(3,4-Dimethoxybenzylidene)morpholinium perchlorate(188).

Morpholine perchlorate (20.0g;0.11mol) was added to a solution of 3,4-dimethoxybenzaldehyde (18.3g;0.11mol) in dry benzene ($250cm^3$). The mixture was heated under reflux conditions for six hours whilst water was removed with the aid of a Dean-Stark trap. Stirring was continued throughout this time. The resulting precipitate was washed with diethyl ether ($200cm^3$) and recrystallised from acetonitrile ($100cm^3$) to yield the product as pale yellow needles (31.7g;86%).

m.p. 210°C.

^1H n.m.r. $\delta(D_2O)$; 9.58(s, 1H, NCH), 7.38(dd, 1H, ArH, 6-position, J= 8, $2H_3$), 7.13(d, 1H, ArH, 2-position, J= $2H_3$), 6.93(d, 1H, ArH, 5-position), 4.1-3.9 (m, 4H, 2x OCH_2), 3,85, 3.76(2s, 6H, 2x OCH_3) 3.4-3.25(m, 4H, 2x NCH_2).

i.r. (nujol mull), $\bar{\nu}_{max}$, cm^{-1}; 1645(C=N), 1090(ClO_4^-).

u.v. λ_{max}, nm (ξ, $1mol^{-1}cm^{-1}$), 228.5(16,400), 273.5(10,600), 306(8,400).

Mass spectrum; m/e (rel. abundance), 236(12)M, 151(47), 87(100).

Analysis; found: C, 46.8; H, 5.5; N, 3.9. $C_{13}H_{18}ClNO_7$ requires C, 46.6; H, 5.4; N, 4.2%.

1,4-Dihydro-4-(α-hydroxy-3-methoxybenzyl)-6,7-dimethoxy-2-methyl-3(2H)-isoquinolinone(191).

The whole of the following reaction sequence was carried out under an atmosphere of dry nitrogen and reagents were added *via* a septum cap with the aid of a glass syringe. The reaction mixture was maintained at 0°C throughout until one hour after the final addition when the temperature was allowed to rise slowly to that of the laboratory. n-Butyl lithium (0.42g;0.0073mol, $2.5cm^3$ of 15% solution in n-hexane) was added dropwise to a stirred solution of diisopropylamine (0.72g;0.0072mol) in dry tetrahydrofuran ($5.0cm^3$). The solution was then stirred for half an hour. Hexamethylphosphoric triamide (1.2g;0.0072mol) in dry tetrahydrofuran ($5cm^3$) was then added and after an interval of half an hour 1,4-dihydro-6,7-dimethoxy-2-methyl-3(2H)-isoquinolinone (1.5g; 0.0068mol) in dry tetrahydrofuran ($25.0cm^3$) was added dropwise over a period of half an hour. After allowing the the mixture to stir for a further half hour 3-methoxybenzaldehyde (0.93g;0.0068mol) in dry tetrahydrofuran ($20cm^3$) was added over a period of approximately one hour. The temperature of the mixture was then allowed to rise to ambient temperature

and the mixture was left stirring overnight. The resulting precipitate was removed by filtration to yield the product as a white solid (1.7g;73%). Recrystallisation of the product was not possible as all attempts led to decomposition to 6,7-dimethoxy-1,3,4-isoquinolinetrione. Short column chromatography[161] using silica gel (100g) in a 2.5cm diameter column and 5% methanol in dichloromethane as the elutant led to the isolation of a pure material (0.95g;41%).

m.p. 176.5-177.5°C.

^{1}H n.m.r. $\delta(CDCl_3)$, 7.05(t, 1H, 5-position of benzyl substituent, $J = 7H_3$), 6.75(m, 1H, 6-position of benzyl substituent), 6.57(s, 1H, 5-position), 6.5-6.3(m, 3H, 3x ArH), 5.10(dd⟶d(on addition of D_2O), 1H, CHOH, $J_{H,OH} = 9H_3$, $J_{HA} = 4H_3$), 4.83(d, 1H, OH, $J = 7H_3$) 3.98(br., 1H, CHCHOH) 3.82(5, 6H, 2x OCH_3, 6,7-positions), 3.62(s, 3H, OCH_3), 3.82, 3.33(d,dd, 2H, $ArCH_2$, $J = 4H_3$, $16H_3$), 2.89(s, 3H, NCH_3). p.161.

i.r. (0.5% $CHBr_3$) $\bar{\nu}_{max}$, cm^{-1}; 3590 (free OH, weak), 3400 (bonded OH, strong, intramolecular), 1628 (CO), 2840, 1260, 1038 ($ArOCH_3$). p.162.

u.v. λ_{max}, nm (ξ, $1mol^{-1}cm^{-1}$); 226(sh., 14,000), 275(sh., 4,500), 281.5(5,200), 291(sh., 3250).

Mass spectrum; m/e (rel. abundance,%), 339(73)M-18, 220(100), 136(55).

Analysis; found: C, 67.5; H, 6.6; N, 3.7. $C_{20}H_{23}NO_5$ requires C, 67.2; H, 6.5, N, 3.9%.

6,7-Dimethoxy-2-methyl-1,3,4(2H)-isoquinolinetrione(192).

N-Methyl-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl) propionamide (2.0g;0.006mol) was dissolved in glacial acetic acid ($30cm^3$) and a solution of chromium trioxide in glacial acetic acid ($20cm^3$ of a 10% solution) was added dropwise over a period of one hour and the mixture left stirring for four hours. After this time water ($150cm^3$) was added and the yellow precipitate formed removed by filtration and recrystallised from ethanol ($100cm^3$) to yield bright yellow needles of the product (0.96g;64%).

m.p. 273-275°C, lit., 275-276°C[167].

^{1}H n.m.r. $\delta((CH_3)_2SO)$; 7.59(s, 1H, ArH), 7.47(s, 1H, ArH), 3.95(s, 3H, OCH_3), 3.91(s, 3H, OCH_3), 3.23(s, 3H, NCH_3).

i.r. (nujol mull) $\bar{\nu}_{max}$, cm^{-1}; 1725, 1695, 1670.

u.v. λ_{max}, nm (ξ, $1mol^{-1}cm^{-1}$); 223(7,710), 267(17,800), 340 (2,850), 364(2,820).

Mass spectrum; m/e (rel. abundance,%) 249(100)M, 221(90), 177(86), 164(90), 136(69).

metastables; 196.1(249-221), 141.8(221-177), 112.8(164-136), 108.0(249-164).

Analysis; found: C, 57.7; H, 4.7; N, 5.7. $C_{12}H_{11}NO_5$ requires C, 57.8; H, 4.5; N, 5.6%.

3,4-Dimethoxybenzoyl chloride(197).

3,4-Dimethoxybenzoic acid (20.0g;0.11mol) was dissolved in dry toluene ($100cm^3$) and freshly distilled thionyl chloride (19.6g;0.16mol) was added with caution. The mixture was

heated to boiling point over approximately half an hour and further heated under reflux conditions for two hours. The toluene and excess thoinyl chloride were then removed by evaporation under reduced pressure to yield, on cooling, an off-white solid, which was recrystallised from dry toluene ($50cm^3$) to yield white plates (19.6g;89%).
m.p. 76^oC, lit., 70^oC[168].

1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxy-α-(3,4-dimethoxy-benzoyloxy)benzylidene)-2-methyl-3(2H)-isoquinolinone(198).

The whole of the following reaction sequence was carried out under an atmosphere of dry nitrogen and reagents were added *via* a septum cap with the aid of a glass syringe. The reaction mixture was maintained at 0^oC throughout until one hour after the final addition when the temperature was allowed to rise slowly to that of the laboratory. n-Butyl lithium (0.42g;0.0072mol, $2.5cm^3$ of a 15% solution in hexane) was added, dropwise, to a stirred solution of diisopropylamine (0.72g; 0.0072mol) in dry tetrahydrofuran ($5.0cm^3$). The solution was then stirred for half an hour. Hexamethylphosphoric triamide (1.2g;0.0072mol) in dry tetrahydrofuran ($5.0cm^3$) was then added and after an interval of half an hour 1,4-dihyro-6,7-dimethoxy-2-methyl-3(2H)-isoquinolinone (1.5g;0.0068mol) in dry tetrahydrofuran ($25cm^3$) was added dropwise over a period of approximately half an hour. After leaving the mixture to stir for a further half hour 3,4-dimethoxybenzoyl chloride (3.0g;0.014mol) in dry tetrahydrofuran ($20cm^3$) was added over a period of approximately one hour . The temperature of the mixture was then allowed to rise to ambient temperature and

the mixture left stirring overnight . The pale yellow precipitate produced was then isolated by filtration and recrystallisation from dimethyl suphoxide ($30cm^3$) to yield pale yellow needles (2.65g;71%).

m.p. 207-209°C

^{1}H n.m.r. $\delta(CDCl_3)$; 7.94(dd, 1H, J= 2, $6H_3$, 6-position ArCO), 7.72(d, 1H, J=$2H_3$, 2-position ArCO), 7.2-6.5(m, 6H, 6x ArH), 4.48(s, 2H, $ArCH_2$), 3.95(s, 6H, 2x OCH_3), 3.88,3,85,3,69, 3.38(4s, 4x 3H, 4x OCH_3), 3.08(s, 3H, NCH_3).p.163.

i.r. (nujol mull) $\bar{\nu}_{max}$, cm^{-1}; 1740(ester carbonyl), 1645 (lactam carbonyl), 1600, 1510,p.164.

u.v. λ_{max}, nm (ξ, $1mol^{-1}cm^{-1}$); 223(26,400), 260(22,800), 300(11,800) shoulder.

Mass spectrum; m/e (rel. abundance,%), 549(42)M, 385(15), 247(10), 165(100).

Analysis; found: C, 65.7; H, 6.3; N, 2.7. $C_{30}H_{31}NO_9$ requires C, 65.6; H, 5.7; N, 2.6%.

Ethyl 3,4-dimethoxybenzoate.

3,4-Dimethoxybenzoic acid (18.2g;0.1mol) was heated with absolute ethanol ($60cm^3$) and concentrated sulphuric acid ($1.5cm^3$) under reflux conditions for four hours. The mixture was then allowed to cool, diluted with water ($200cm^3$) and extracted with dichloromethane (3x $40cm^3$). The combined extracts were washed with aqueous sodium hydroxide solution ($40cm^3$; 2M), water (2x $40cm^3$), dried over sodium sulphate and evaporated under reduced pressure producing a colourless oil

which was dissolved in absolute ethanol ($30cm^3$) and cooled to -10^oC. After "scratching" with a glass rod the product was obtained as colurless needles, which were then washed with ice cold absloute ethanol ($20cm^3$) and dried at 30^oC under vacuum, (13.3g;63%).

m.p. 40-42°C, lit., 43-44°C[168].

4-Nitrophenyl 3,4-dimethoxybenzoate.

A solution of 3,4-dimethoxybenzoyl chloride (20.1g;0.1mol) in dry tetrahydrofuran ($150cm^3$) was added dropwise over a period of approximately half an hour to a stirred solution of 4-nitrophenol (13.9g;0.1mol) in dry pyridine ($100cm^3$). The mixture was stirred for a further one hour and the resulting precipitate removed by filtration, washed with aqueous hydrochloric acid ($100cm^3$, 2M), water (2x 100 cm^3) and recrystallised from tetrahydrofuran ($300cm^3$) to produce colourless needles (22.4g;74%).

m.p. 68-69°C, lit., 70°C[168].

^1H n.m.r. $\delta(CDCl_3)$ 8.28(d, 2H, J= $9H_3$, 2x ArH, o-NO_2), 7.98-7.80(m, 1H, meta split doublet, 6-position on veratryl ring), 7.65(d, 1H, J= $2H_3$, 1-position), 7.4(d, 2H, m-NO_2, J= $9H_3$), 6.97(d, 1H, J= $8H_3$, 5-position), 3.96(s, 6H, 3x OCH_3).

1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzoyl)-2-methyl-3(2H)-isoquinolinone(200).

A mixture of 1,4-dihydro-6,7-dimethoxy-4-(3,4-dimethoxy)-α-(3,4-dimethoxybenzoyloxy)benzylidene)-2-methyl-3(2H)-

isoquinolinone (3.3g;0.0060mol) and glacial acetic acid ($50cm^3$) was heated under reflux conditions for a period of eight hours. After this time the reaction mixture was cooled and added to water ($150cm^3$) and the resulting solution extracted with dichloromethane (3x $50cm^3$). The combined extracts were washed with saturated sodium bicarbonate solution until no further evolution of carbon dioxide was observed, water ($50cm^3$), dried using magnesium sulphate and the solvent removed by evaporation under reduced pressure to yield a colourless oil. The oil was dissolved in hot ethanol ($20cm^3$) and the product obtained, on cooling, as a white solid, (1.65g;71%).

m.p. 149-150°C.

^{1}H n.m.r. $\delta(CDCl_3)$, 8.0(dd, 1H, J= 8, $2H_3$, 6-position ArCO), 7.70(d, 1H, J= $2H_3$, 2-position ArCO), 6.98(d, 1H, J= $8H_3$, 5-position ArCO), 6.78(s, 1H, ArH 5-position), 6.54(s, 1H, ArH 8-position), 5.52(s, 1H, ArCHCO), 4.92,4.28(ABq, 2H, J= $15H_3$, $ArCH_2N$), 3.97, 3.90, 3.87 , 3.75(4s, 12H, 4x OCH_3), 3.12(s, 3H, NCH_3), 3.44(impurity). p.165.

i.r. (0.5% $CHBr_3$), $\bar{\upsilon}_{max}$, cm^{-1}; 1670 sh(CO), 1645(amide CO), 1665, 1020 ($ArOCH_3$).p.166.

No evidence of enol form.

u.v. λ_{max}, nm (ξ, $1mol^{-1}cm^{-1}$); 241(8,520), 280(9,570), 307(8,080).

Mass spectrum; m/e (rel. abundance,%), 385(36)M, 247(19), 220(16), 165(100)

metastables, 158.5(385-247).

Analysis; found: C, 65.2; H, 5.9; N, 3.8. $C_{21}H_{23}NO_6$ requires C, 65.4; H, 6.0; N, 3.6%.

1,4-Dihydro-4-(α-hydroxy-3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-3(2H)-isoquinolinone(201).

Sodium borohydride (0.1g;0.0025mol) was added to a solution of 1,4-dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzoyl)-2-methyl-3(2H)-isoquinolinone (0.10g;0.00026mol) in 95% ethanol ($50cm^3$) and the mixture stirred at room temperature for two hours. 2M Hydrochloric acid ($50cm^3$) was then added and the mixture extracted with dichloromethane (3x $25cm^3$). The combined organic extracts were washed with water ($20cm^3$), dried over magnesium sulphate and evaporated under reduced pressure to yield a colourless oil which was crystallised from ethanol ($5cm^3$) to yield the product as colourless prisms (0.08g;79%).

m.p. 182-183.5°C.

^{1}H n.m.r. δ($CDCl_3$), 6.65(d, 1H, 5-position of 4-benzyl subs., J= 9H_3), 6.60(s, 1H, ArH, isoquinolone ring), 6.39 (s, 1H, ArH, isoquinolone ring), 6.4-6.2(m, 2H, 2x ArH), 5.02,(dd→d(on addition of D_2O), 1H, CHOH, $J_{H,OH}$= 9H_3, J_{HA}= 4.2H_3), 4.98(s, 1H, OH), 3.94(m, 1H, CHCHOH), 3.8-3.7(m, 9H, 3x OCH_3), 3.53 (s, 3H, OCH_3), 3.8-3.7, 3.20(m, 2H, dd, $ArCH_2$, J= 4,24H_3) 2.82(s, 3H, NCH_3).

i.r. (0.5% $CHBr_3$) $\bar{\upsilon}_{max}$, cm^{-1}; 3400(bonded OH), 1620(CO), 2840, 1260, 1038($ArOCH_3$).

u.v. λ_{max}, nm (ξ, $1mol^{-1}cm^{-1}$); 239(sh., 8,700), 283.5(4,300).

Mass spectrum; m/e (rel. abundance,%), 369(58)M-18, 220(100), 166(78).

metastables, 131.2(369-220).

Analysis; found: C, 65.3; H, 6.6; N, 3.4. $C_{21}H_{25}NO_6$ requires C, 65.1; H, 6.5; N, 3.6%.

3,4-Dimethoxybenzylideneaminoacetaldehyde dimethylacetal(208)[111].

Aminoacetaldehyde dimethylacetal (10.5g;0.1mol) and 3,4-dimethoxybenzaldehyde (16.6g;0.1mol) were dissolved in dry benzene (100cm^3) and the mixture was heated under reflux conditions for five hours with constant removal of water using a Dean and Stark apparatus. The solvent was then removed by evaporation under reduced pressure to yield a colourless oil. The oil was then dissolved in anhydrous ethanol (50cm^3) and cooled to approximately -10°C whereupon crystals of the product began to form after "scratching" with a glass rod. The solid was washed with ice cold diethyl ether (3x 10cm^3), yielding small, colourless needles (21.2g;83%) 60°-80°, petroleum spirit (1000cm^3) was sometimes used for crystallisation of the oil instead of anhydrous ethanol. m.p. 57-58°C.

All spectral details agreed with those previously reported[111].

3,4-Dimethoxybenzylaminoacetaldehyde dimethylacetal(209)[111].

3,4-Dimethoxybenzylideneaminoacetaldehyde dimethylacetal (25.3g;0.1mol) was dissolved in 95% ethanol (150cm^3) and

freshly ground sodium borohydride (8.0g;0.2mol) was added, portionwise. The mixture was stirred overnight at room temperature. Water ($300cm^3$) was then added to the mixture which was subsequently extracted with dichloromethane (3x $50cm^3$). The combined extracts were then washed with water (2x $100cm^3$), dried using sodium sulphate and the solvent evaporated under reduced pressure to yield a colourless oil. The resulting oil was then distilled (150^o-160^oC, 0.6mm) to yield a colourless oil (17.3g;67%). If the temperature of the oil bath used in the distillation was allowed to rise above 200^oC, the yield was substantially reduced. This oil was then used for further reaction but if left to stand the product was obtained as long colourless neeedles. This compound has not previously been reported as a solid and thus a full characterisation is given below.

m.p. 42-43°C.

^1H n.m.r. $\delta(CDCl_3)$, 7.30(d, 1H, ArH, 1-position), 7.0-6.7 (m, 3H(2H an addition of D_2O), 2x ArH + NH), 4.70 (t, 1H, CH_2CH, J= 7Hz), 4.0-3.8(3s, 8H, $ArCH_2$ + 2x $ArOCH_3$), 3.40(s, 6H, 2x OCH_3), 2.80(d, 2H, CH_2CH, J= 7Hz)

i.r. (0.5% $CHBr_3$) $\bar{\nu}_{max}$, cm^{-1}, 3230, 2700-2000 (bonded NH), 1260, 1043, 1043, 1024($ArOCH_3$).

All other spectra as previously reported[111].

Analysis; found: C, 61.5; H, 8.3; N, 5.2. $C_{13}H_{21}NO_4$ requires C, 61.2; H, 8.2; N, 5.5%.

1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzylidene)isoquinolinium chloride(210).

3,4-Dimethoxybenzaldehyde (18.3g;0.11mol) freshly recrystallised from absolute ethanol and freshly distilled 3,4-dimethoxybenzylaminoacetaldehyde dimethyl acetal (25.5g; 0.10mol) were dissolved in ethanol ($40cm^3$) and the mixture heated on a steam bath for two hours. Water ($40cm^3$)was then added and the mixture set aside. After two to four days the product appeared as a red crystalline solid. The solid was recrystallised form ethanol ($50cm^3$), taking care to avoid excessive heating*, to yield fine red needles (28.7g;76%). The product was dried over P_2O_5 under reduced pressure.

m.p. 185°C(decomp.).

^{1}H n.m.r. $\delta(CDCl_3)$, 8.65(s, 1H, NHCH), 8.3(s, 1H, removed by deuteriation, NH), 7.35-6.55(m, 6H, 5x ArH + olefinic H), 4.90(br.s, 2H, $ArCH_2$), 4.05-3.75(m, 12H, 4x OCH_3).

i.r. (nujol mull) $\bar{\nu}_{max}$, cm^{-1}; 3350(br., NH), 1650(C=N), 1605, 1590, 1370.

Analysis (as the isomerised base 6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline), found: C, 70.9; H, 6.2; N, 4.2. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.2; N, 4.1%.

*Footnote

It is important not to heat this compound above 60°C since isomerization occurs.

6,7-Dimethoxy-3-(3,4-dimethoxybenzyl)isoquinoline(211)[111].

1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzylidene) isoquinolinium chloride (20.0g;0.053mol) was dissolved in ethanol ($200cm^3$) and an hydrous potassium carbonate(20g) was

added. The mixture was heated under reflux conditions, while being continuously stirred for four hours and was then filtered to remove excess potassium carbonate. The solvent was then removed by evaporation under reduced pressure and the residue dissolved in dichloromethane ($100cm^3$). This solution was then washed with water (2x $50cm^3$) dried using magnesium sulphate and the solvent removed by evaporation under reduced pressure. The resultant oil was then dissolved in hot ethanol ($50cm^3$) and left to crystallise. The first crystals to appear were small prisms which proved to be the hydrochloride salt of the required isoquinoline (1.3g;6.5%). After removal of the hydrochloride salt by filtration and "scratching" the filtrate with a glass rod the isoquinoline was precipitated as a white solid which was recrystallised from ethanol ($30cm^3$) to yield fine white needles,(13.3g;74%).

m.p. 127-128°C.

^{1}H n.m.r. $\delta(CDCl_3)$, 9.03(br.s, 1H, ArH, 1-position), 8.33 (s, 1H, ArH, 3-position), 7.20, 7.10(2s, 2x 1H, 2x ArH, 5- and 8-positions), 6.8-6.6(br.s, 3H, 3x ArH), 4.20(s, 2H, $ArCH_2$), 3.95, 3.84, 3.79, 3.72 (4s, 12H, 4x OCH_3).

i.r. (0.5%$CHBr_3$) $\bar{\upsilon}_{max}$, cm^{-1}; 2830, 1250, 1025($ArOCH_3$).

u.v. λ_{max}, nm (ξ,$1mol^{-1}cm^{-1}$); 238(57,600), 282(7,900), 288 (sh., 7,650), 313(3,400), 326.5(3,150).

Mass spectrum, m/e (rel. abundance,%), 339(100)M, 324(19), 308(11).

metastables, 309.7(339-324)

Analysis: found: C, 71.0; 6.2; N, 4.2. $C_{20}H_{21}NO_4$ requires, C, 70.8; H, 6.2; N, 4.1%.

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinolinium iodide(212)[111].

3,4-Dimethoxybenzaldehyde (20.0g;0.12mol) and 3,4-dimethoxybenzylaminoacetaldehyde dimethylacetal (25.5g;0.1mol) were dissolved in ethanol ($40cm^3$). Concentrated hydrochloric acid ($40cm^3$) was then added, portionwise, with cooling and the mixture heated an a steam bath for one hour. Water ($400cm^3$) was then added and the resulting solution extracted with benzene (2x $50cm^3$), to remove excess aldehyde. The aqueous solution was then made strongly basic by the addition of sodium hydroxide solution ($60cm^3$;30%) and heated on a steam bath for 30 minutes. After this time the solution was cooled and extracted with dichloromethane (3x $50cm^3$) and the combined extracts washed with water (2x $50cm^3$) dried using magnesium sulphate and the solvent removed by evaporation under reduced pressure. The crude isoquinoline was thus obtained as an oil which was dissolved in hot acetone ($100cm^3$). Methyl iodide (28.4g;0.2mol) was added to the solution of the isoquinoline and the mixture heated under reflux conditions for 30 minutes. After cooling,the product, a yellow crystalline solid, was removed by filtration and was used without further purification,(20.7g;58%).

m.p. 202-204^{o}C, lit., 204-208^{o}C[111].

all spectral data agree with that previously reported[111].

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinoline(213)[111].

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquin-

olinium iodide (5.3g;0.011mol) was dissolved in 95% ethanol ($200cm^3$). Sodium borohydride (1.7g;0.045mol) was added portionwise and the mixture stirred overnight. After this time 2M hydrochloric acid ($100cm^3$) was added cautiously and, when the mixture had become homogenous, 2M sodium hydroxide solution was added until the solution was alkaline to litmus. After cooling, the solution was extracted with dichloromethane (3x $50cm^3$) and the combined organic extracts were washed with water (2x $50cm^3$), dried over magnesium sulphate and evaporated to yield a colourless oil. This was dissolved in hot ethanol ($15cm^3$) and the product was obtained as a white solid on cooling, (3,51g;91%).

m.p. 96.5-98.0°C, lit., 96-98°C[111].

All spectral details agreed with those reported by Warren[111].

3,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinolinium trifluoroacetate(221).

1',2,3,4-Tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinoline (1.0g;0.0028mol) was electrolysed in a 0.0014M solution of tetra-n-butylammonium tetrafluoroborate in trifluoroacetic acid/dichloromethane (1:3), carbon felt electrodes were used at a potential difference of 1.15V relative to S.C.E. at a current of 100mA for a period of three hours (equivalent to 4.5 Faradays of electricity per mole of substrate). After this time the anolyte was added to water ($200cm^3$) and the resulting solution rendered basic by the addition of concectrated ammonia solution ($50cm^3$). The

basic solution was then extracted with dichloromethane (3x 50cm^3) and the combined extracts washed with water (2x 50cm^3), dried using magnesium sulphate and the solvent evaporated under reduced pressure to produce a colourless oil which was dissolved in hot ethanol (10cm^3) and produced on standing, a white precipitate which was recrystallised from ethanol (10cm^3) to produce the product as a white crystalline solid, (0.38g;29%).

m.p. 204-205°C.

^{1}H n.m.r. δ($CDCl_3$/$(CH_3)_2SO$, 5:1); 9.2(s, 1H, ArC<u>H</u>N), 7.55-7.40(m, 2H, 2x Ar<u>H</u>, 4-benzyl substituent 5 and 6-positions), 7.22(s, 1H, Ar<u>H</u>, 4-benzyl substituent 2-position), 6.65(s, 1H, Ar<u>H</u>), 6.60(s, 1H, Ar<u>H</u>), 3.90(s, 3H, NC<u>H</u>$_3$), 3.84(s, 9H, 3x OC<u>H</u>$_3$), 3.75(s, 3H, OC<u>H</u>$_3$), 3.90-3.45(m, 3H, C<u>H</u>$_2$C<u>H</u>), 2.96(d, 2H, NC<u>H</u>$_2$, <u>J</u>= 8H$_3$).

<u>i.r.</u> (nujol mull) $\bar{\upsilon}_{max}$, cm^{-1}; 1665, 1605, 1560, 1495, 1060.

<u>u.v.</u> λ_{max}, nm(ξ, 1mol^{-1}cm^{-1}); 247(13,000), 295(5,100), 312 (5,400), 355(5,800).

<u>Mass spectrum</u>; <u>m/e</u> (rel. abundance, %); 356(76)M, 206(24), 204(26), 142(100), 127(28).

<u>Analysis</u>; found: C, 58.6; H, 5.8; N, 3.1. $C_{23}H_{26}F_3NO_5$ requires: C, 58.8; H, 5.6; N, 3.0%.

<u>3,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzylidene)-2-methylisoquinolinium trifluoroacetate(222).</u>

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(3,4-diemthoxybenzyl)-2-methylisoquinoline (1.0g;0.0028mol) was electrolysed in a

one molar solution of tetra-n-butylammonium tetrafluoroborate in trifluoroacetic acid/dichloromethane (1:3). Carbon felt electrodes were used at a potential difference of 5.0V relative to S.C.E., at a current of 100mA for a period of three hours (equivalent to 20 Faradays of electricity per mole of substrate). After this time the anolyte was added to water ($200cm^3$) and the resulting solution rendered basic by the addition of concentrated ammonia solution ($50cm^3$). The basic solution was then extracted with dichloromethane (3x $50cm^3$) and the combined extracts washed with water (2x $50cm^3$) dried using magnesium sulphate and the solvent removed by evaporation under reduced pressure. This produced a colourless oil which when dissolved in hot ethanol produced, on standing, a white precipitate which was recrystallised from ethanol ($10cm^3$) to produce the product as a white crystalline solid, (0.29g;22%).

m.p. 195-196°C

^{1}H n.m.r. $\delta(CDCl_3)$, 9.30(s, 1H, NC<u>H</u>), 7.63, 7.57(2s, 2x 1H, 2x Ar<u>H</u> 5- and 8-positions),7.22-7.04(m, 3H, 3x Ar<u>H</u>, benzylidene substituent), 4.35(s, 2H, NC<u>H</u>$_2$), 4.27(s, 3H, NC<u>H</u>$_3$), 3.99, 3.95, 3.78, 3.65(4s, 4x 3H, 3x OC<u>H</u>$_3$).

i.r. (nujol mull) $\bar{\upsilon}_{max}$, cm^{-1}; 1635, 1600, 1590, 1060.

u.v. λ_{max}, nm(ξ, $1mol^{-1}cm^{-1}$); 259(14,500), 313(12,300).

Analysis; found: C, 58.7; H, 5.0; N, 3.1. $C_{23}H_{24}F_3NO_6$ requires C, 59.0; H, 5.2; N, 3.0%.

[E]-α-(3,4-Dimethoxyphenyl)-3,4-dimethoxycinnamonitrile(224)[125].

A solution of 3,4-dimethoxybenzaldehyde (41.5g;0.25mol) in the minimum volume of anhydrous ethanol was added to a solution of (3,4-dimethoxyphenyl)acetonitrile (44.25g; 0.25mol) in the minimum volume of absolute ethanol. Sodium ethoxide solution (50cm^3, 10% solution, 1.67g of sodium, 48.3g of ethanol) was added to the resulting solution, dropwise over a period of half an hour. The solution was stirred mechanically during the addition. The reaction mixture was then cooled in an ice both and resulting solid separated by filtration and recrystallised from methanol (2l) yielding the product as pale yellow needles,(80.3g;90%).
m.p. 154-155°C; lit., 155.5°C[123].

All spectral details were as previously reported[123].

2,3-Bis-(3,4-dimethoxyphenyl)propylamine(225)[123].

A solution of [E]-α-(3,4-dimethoxyphenyl)-3,4-dimethoxycinnamonitrile(4.0g;0.0124mol) in methanol (500cm^3) was hydrogenated at a temperature of 80°C, a pressure of 12atm and in the presence of Raney nickel (3.0g)[170] for five hours using a stainless steel vessel. The catalyst was then removed by filtration, great care having been taken to ensure that it remained covered by solvent at all times prior to its neutralization with 2M nitric acid. The solvent was then removed by evaporation under reduced pressure to produce a white solid which was recrystallised from ethanol (10cm^3) to produce the product as a white crystalline solid,(3.1g;76%).
m.p. 51-52°C, lit., 52-52°C[123].

All spectral details were as previously reported[123].

N-(2,3-Bis-(3,4-dimethoxyphenyl)propyl)formamide(226).

A mixture of 2,3-bis-(3,4-dimethoxyphenyl)propylamine (0.6g;0.0018mol) and formic acid (0.83g;0.018mol)was heated under an atmosphere of dry nitrogen to a temperature of 200°C by means of an oil bath. After three hours at this temperature the mixture was dissolved in dichloromethane ($20cm^3$). The solution was then washed with sodium bicarbonate solution until no further evolution of carbon dioxide was observed, water ($50cm^3$), dried using magnesium sulphate and the solvent removed by evaporation under reduced pressure. This produced the crude amide as a colourless oil which was further purified by short column chromatography[171] using silica gel and 5%methanol in dichloromethane as the elutent. This produced the product as a colourless oil (0.27g;42%).

b.p. 256°C (decomp.)

^{1}H n.m.r. $\delta(CDCl_3)$; 8.05(d, 1H, NHCHO, J= $1H_3$), 6.90-6.40 (m, 6H, Aromatics), 5.5(br.s, 1H, NHCHO), 3.9-3.7(m, 12H, 4x OCH_3), 3.6-2.6(m, 5H, aliphatic protons).

i.r. (0.5% $CHBr_3$) $\bar{\upsilon}_{max}$, cm^{-1}; 3420(NH), 1678(amide I), 1512 (amide II), 2830, 1258, 1025(-OCH_3).

u.v. λ_{max}, nm (ε, $1mol^{-1}cm^{-1}$); 229.5(15,400), 279.5(5,750), 286(sh)(4,850).

Mass spectrum; m/e (rel. abundance,%); 359(14)M, 3.4(14), 302(16), 165(16), 151(100).

Analysis; found: C, 6.7; H, 7.2; N, 3.5. $C_{20}H_{25}NO_5$ requires

C, 66.9; H, 7.0; N, 3.9%.

2-Benzyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinolinium bromide(229).

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline (7.3g; 0.022mol) was dissolved in hot acetone ($40cm^3$) and benzyl bromide (4.2g; 0.024mol) was added. The mixture was heated under reflux conditions on a steam bath for two hours. After cooling the precipitate was isolated and recrystallised from ethanol ($20cm^3$) to give the product as colourless prisms, (9.8g;87%).

m.p. 127-130°C.

^{1}H n.m.r. $\delta((CD_3)_2SO)$, 9.97(s, 1H ArH, 1-position), 8.90 (s, 1H, 3-position), 7.97(s, 1H, 8-position), 7.77(s, 1H, 5-position), 7.8-7.5(m, 5H,2-benzyl substituent), 7.1(br.s, 1H, 2-position of 4-benzyl substituent), 6.98(s, 2H, 5- and 6-positions of 4-benzyl substituent), 6.02(s, 2H, $PhCH_2N$), 4.55 (br.s, 2H, $ArCH_2$), 4.13, 4.04, 3.77, 3.73(4s, 12H, 4x OCH_3).

i.r. (0.5% $CHBr_3$), $\bar{\nu}_{max}$, cm^{-1}, 2840, 1260, 1025($ArOCH_3$).

u.v. λ_{max}, nm(ε, $1mol^{-1}cm^{-1}$); 258(58,300), 285(sh)(5,950), 319(12,400).

Mass spectrum; m/e (rel. abundance, %), 339(29)M-91, 91(100).

Analysis; found: C, 63.6; H, 5.5; N, 2.6. $C_{27}H_{28}NO_4Br$ requires, C, 63.5; H, 5.5; N, 2.7%.

2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline(230).

2-Benzyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinolinium bromide (3.2g;0.0063mol) was dissolved in 95% ethanol ($150cm^3$). Sodium borohydride (1.0g;0.026mol) was added portionwise. After stirring overnight 2M hydrochloric acid ($100cm^3$) was added cautiously and when the mixture had become homogenous 2M sodium hydroxide solution was added until the solution was alkaline to litmus. After cooling, the solution was extracted with dichloromethane (3x $50cm^3$) and the combined organic extracts were washed with water (2x $50cm^3$), dried over magnesium sulphate and evaporated under reduced pressure to yield a colourless oil. This was dissolved in hot ethanol ($10cm^3$) and the product was formed as a white solid on cooling, (2.2g;81%).

m.p. 106-107°C

^{1}H n.m.r. $\delta(CDCl_3)$, 7.5-7.2(m, 5H, 5x ArH, 2-benzyl substituent), 6.8-6.5)m, 5H, 5x ArH), 3.9-3.5(3s, 12H, 4x OCH_3), 3.6(br.s, 2H, $ArCH_2N$), 3.7, 3.3(ABq, 2H, J= 18H_3, $PhCH_2N$), 3.0-2.3(m, 5H, $ArCH_2CHCH_2N$).

i.r. (nujol mull) υ_{max}, cm^{-1}, 1605, 1590, 1510, 1135.

u.v. λ_{max}, nm (ε, $1mol^{-1}cm^{-1}$); 239(8,330), 283(6,710).

Mass spectrum, m/e (rel. abundance,%), 433(12)M, 432(21), 342(100), 314(10), 299(16), 281(62), 151(21).

metastables, 270.1(433-342), 284.7(314-299).

Analysis; found: C, 71.0; H, 6.2; N, 4.2. $C_{27}H_{31}NO_4$ requires C, 70.8; H, 6.2; N, 4.1%.

The hydrochloride was prepared by adding a solution of

hydrogen chloride in diethyl ether to a solution of the base (3.7g;0.0085mol) in toluene ($30cm^3$) until no further precipitate was observed and recrystallising the product from methanol ($10cm^3$) to yield the salt as fine needles,(3.28g; 82%).

m.p. 218-219°C

^{1}H n.m.r. poor resolution spectrum abtained . The sample was shaken with sodium bicarbonate solution to obtain a spectrum of the sample as the free base. This was in agreement with that reported above.

i.r. (0.5% $CHBr_3$), $\bar{\upsilon}_{max}$, cm^{-1}, 2500-2200(br., NH^+), 2830, 1260, 1025.

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline(228).

2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline hydrochloride salt (0.40g;0.001mol) was dissolved in absolute ethanol ($200cm^3$) and hydrogenated at atmospheric pressure over 10% palladium on charcoal (0.05g) for three hours. The catalyst was then filtered off and the solvent removed by evaporation under reduced pressure to yield a white solid which was recrystallised from ethanol ($5cm^3$) to yield the product as a white solid,(0.31g;76%).

m.p. 136-140°C.

^{1}H n.m.r. $\delta(CDCl_3)$, 6.9-6.6(m, 3H, 3x ArH, 4-benzyl substituent), 6.50(s, 2H, 2x ArH), 3.9-3.7(m, 14H, 4x OCH_3 + $ArCH_2N$), 3.0-2.8(m, 5H, rest).

i.r. (of hydrochloride salt)(0.5%$CHBr_3$) $\bar{\upsilon}_{max}$, cm^{-1}, 2800-

2300(NH_2^+), 2840, 1260, 1028($ArOCH_3$).

u.v. λ_{max}, nm(ε, $lmol^{-1}cm^{-1}$); 233(15,350), 282(6,300).

Mass spectrum, m/e (rel. abundance,%) 343(32)M, 192(100), 161(16), 151(16).

metastables, 135.0(192-161).

Analysis; found: C, 62.8; H, 7.2; N, 3.5. $C_{20}H_{25}NO_4HCl$ requires C, 63.2; H, 6.9; N, 3.7%.

2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline(229).

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzl)isoquinoline hydrochloride salt (1.60g;0.0047mol) was dissolved in chloroform ($50cm^3$) and washed with saturated sodium bicarbonate solution until no further evolution of carbon dioxide was evident. The solution was washed with water ($50cm^3$) and dried over magnesium sulphate.

To the solution of free base was added anhydrous potassium carbonate (1.0g) and trifluoroacetic anhydride (2.1g;0.01mol). The mixture was stirred at room temperature for four hours protected by a calcium chloride drying tube. The chloroform solution was then washed with water (2x $50cm^3$) dried over magnesium sulphate and evaporated under reduced pressure to yield a white solid which was recrystallised from ethanol ($10cm^3$) to yield the product as white floretts,(1.4g;63%). m.p. 98.5-99.5°C.

^1H n.m.r. $\delta(CDCl_3)$; 6.9-6.5(m, 3H, 3x ArH) 4-benzyl substituent), 6.35(s, 2H, 2x ArH), 4.85, 4.60(ABq, 2H, $ArCH_2N$, J= 20 H_3) 4.55, 4.0-2.7(m, 17H, rest)

p. 167 to 169.

i.r. (0.5% $CHBr_3$) $\bar{\upsilon}_{max}$, cm^{-1}, 1690(CO), 2840, 1260, 1028 ($ArOCH_3$) p.170.

u.v. λ_{max}, nm (ε, $1mol^{-1}cm^{-1}$); 230(sh.), 283(6,600).

Mass spectrum; m/e (rel. abundance,%), 439(23)M, 288(35), 151(100).

Analysis; found: C, 60.2; H, 5.6; N, 2.9. $C_{22}H_{24}F_3NO_5$ requires C, 60.1; H, 5.5; N, 3.2%.

Electrolysis of 2-trifluroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline(229).

The substrate (0.50g;0.0011mol) was electrolysed in acetonitrile using sodium perchlorate (0.2M) as the supporting electrolyte. The potential drop at the anode was 1.1V throughout the electrolysis and the current dropped from 500mA to ≈10mA over a period of three hours, after which time electrolysis was stopped . The anolyte was added to water ($200cm^3$) and extracted with dichloromethane (3x $50cm^3$). The combined extracts were washed with saturated sodium chloride solution (2x $50cm^3$), water ($50cm^3$), dried over magnesium sulphate and evaporated under reduced pressure to yield a brown tarry mass. This was boiled with activated charcoal (1.0g) in ethanol ($50cm^3$) to yield, after evaporation under reduced pressure, a brown gum, (0.07g; 14% of starting material). This was shown by thin layer chromotography (silica and alumina, acetone/petroleum ether, 1:1) to be a multicomponent mixture.

i.r. (film) $\bar{\upsilon}_{max}$, cm^{-1}, 1670-1620(br.)

Tetra(n-butyl)ammonium tetrafluoroborate.

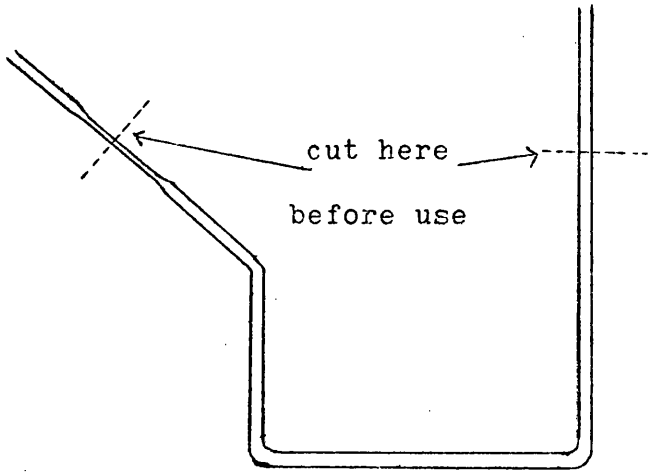
Tetra(n-butyl)ammonium iodide (36.9g;0.1mol) was dissolved in ethanol ($100cm^3$) and added to a solution of sodium tetrafluoroborate (11g;0.1mol) in water ($100cm^3$). The resulting solution was extracted with dichloromethane ($3x\ 60cm^3$) and the combined extracts washed with water ($3x\ 50cm^3$), dried over magnesium sulphate and the solvent partially removed by evaporation under reduced pressure. When about 90% of the solvent had been removed, dry diethyl ether ($50cm^3$)was added to precipitate the product which was, after allowing the mixture to stand for half an hour, isolated by filtration, washed with ice cold diethyl ether ($2x\ 50cm^3$) and dried at 60^oC under vacuum, overnight. The product was obtained as white needles, (25.4g;77%).

m.p. 162-164^oC.

^1H n.m.r $\delta(CDCl_3)$; 3.32(t, 2H, $\underline{J}=8H_3$, $NC\underline{H}_2CH_2$), 1.9-1.3 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2$), 1.08(t, 3H, $\underline{J}= 6H_3$, $CH_2C\underline{H}_3$).

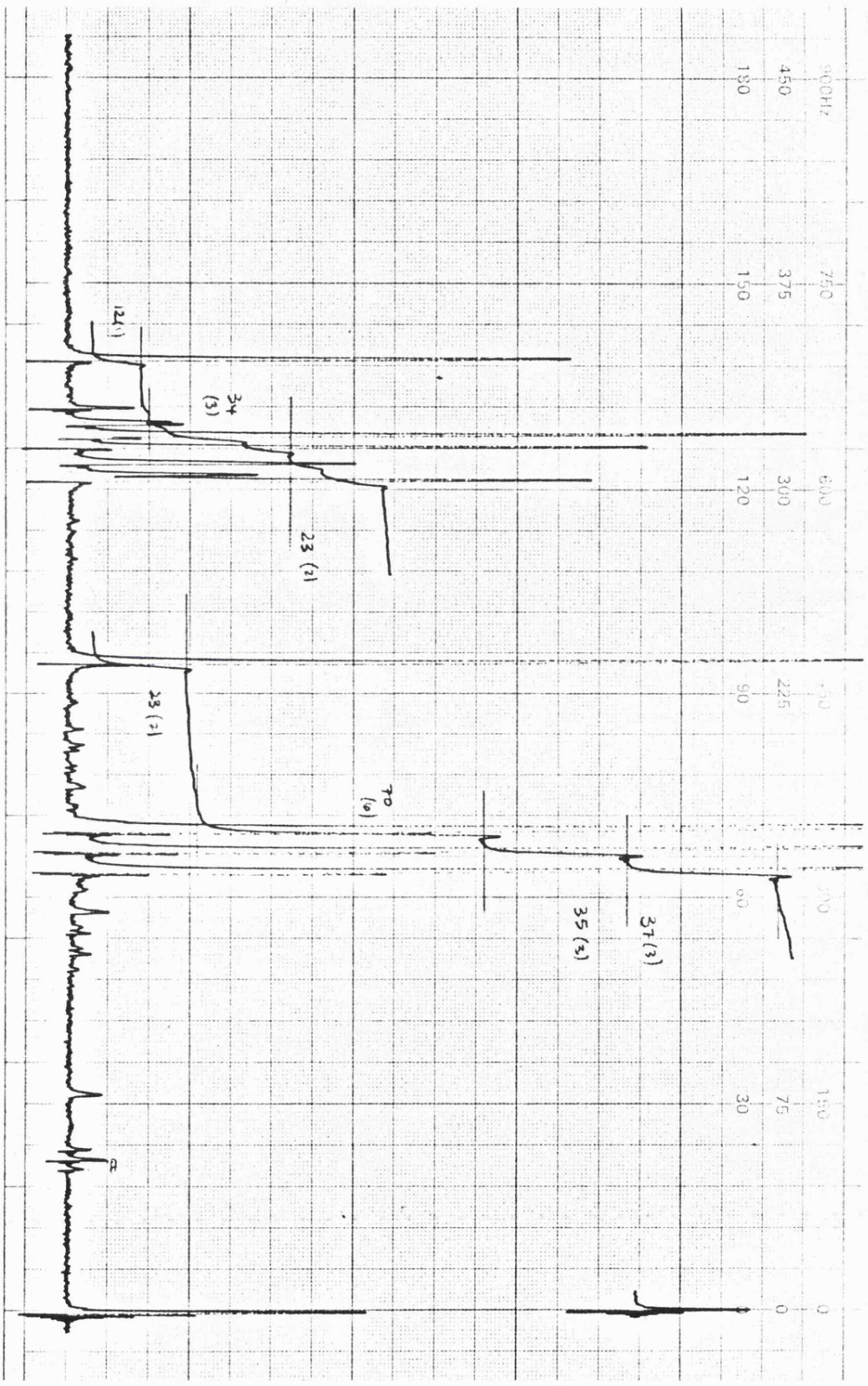
i.r. (nujol mull) $\bar{\nu}_{max}$, cm^{-1}; 1070(BF_4^-).

Preparation of salt bridges.

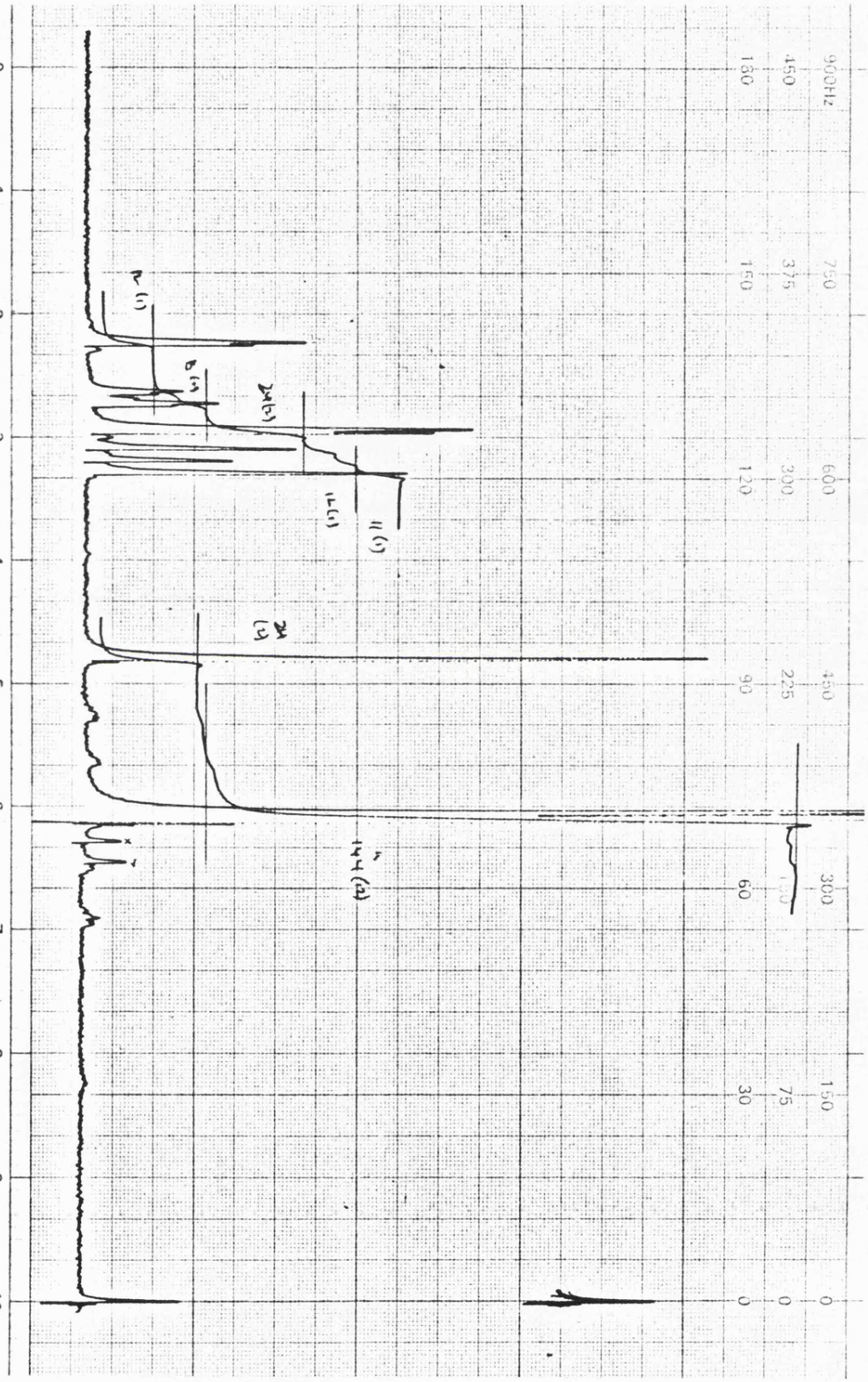


Glass tubing (6mm O.D.) was bent and drawn into approximately the shape depicted in the above diagram. A mixture of agar-agar (3.0g), potassium chloride (30.0g) and water ($100cm^3$) was heated on a steam bath for six hours. The mixture, while still hot, was used to fill the previously warmed, glass tubing. A $10cm^3$ pippette and filler pump were used to transfer the liquid and care was taken not to allow air bubbles to be trapped in the tubes. The filled tubes were left in a vertical position until the jelly had set, after which time they were stored with both ends immersed in saturated aqueous potassium chloride solution. Immediately prior to use the tubes were removed from the storage solution and cut as shown in the diagram.

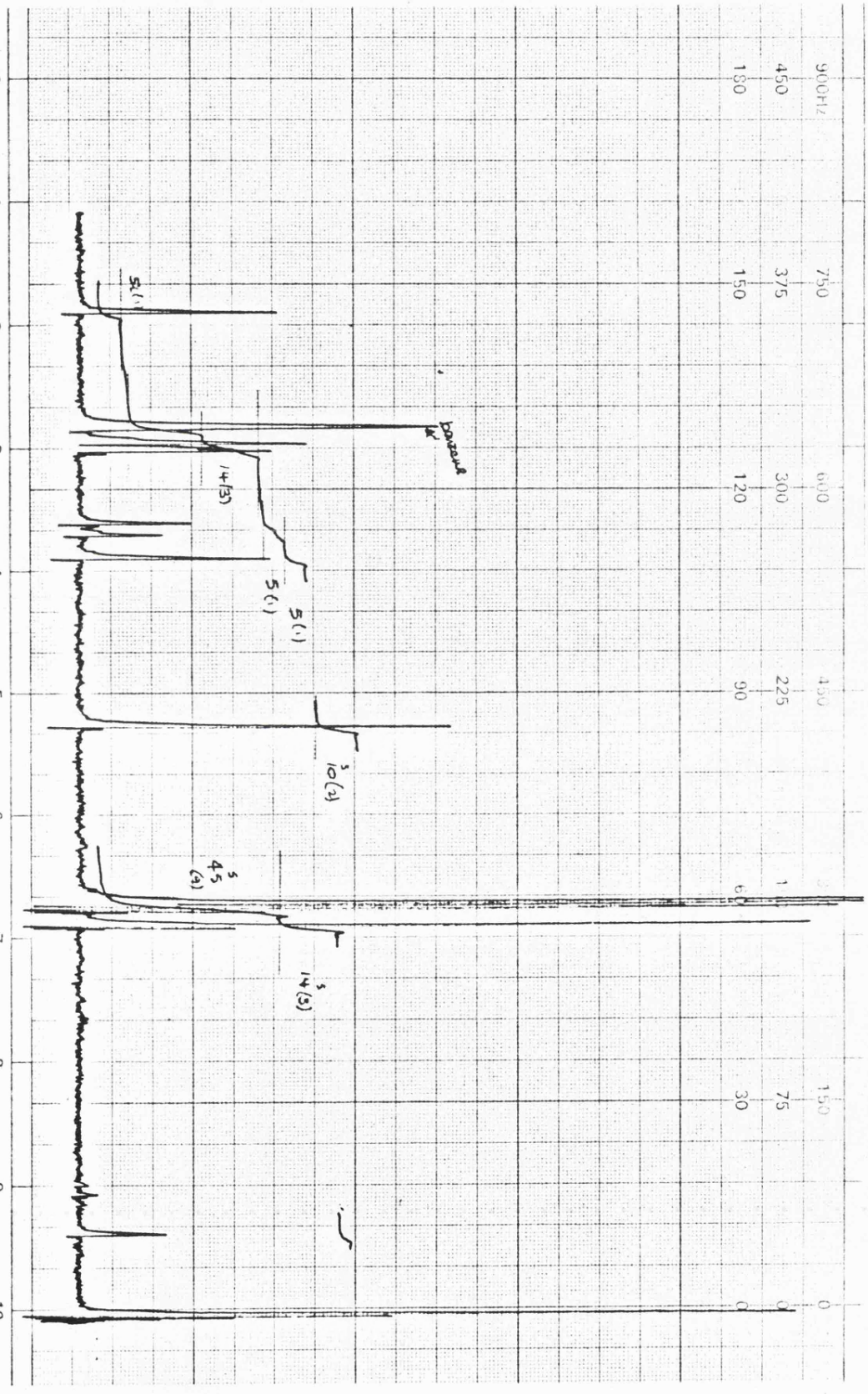
APPENDIX



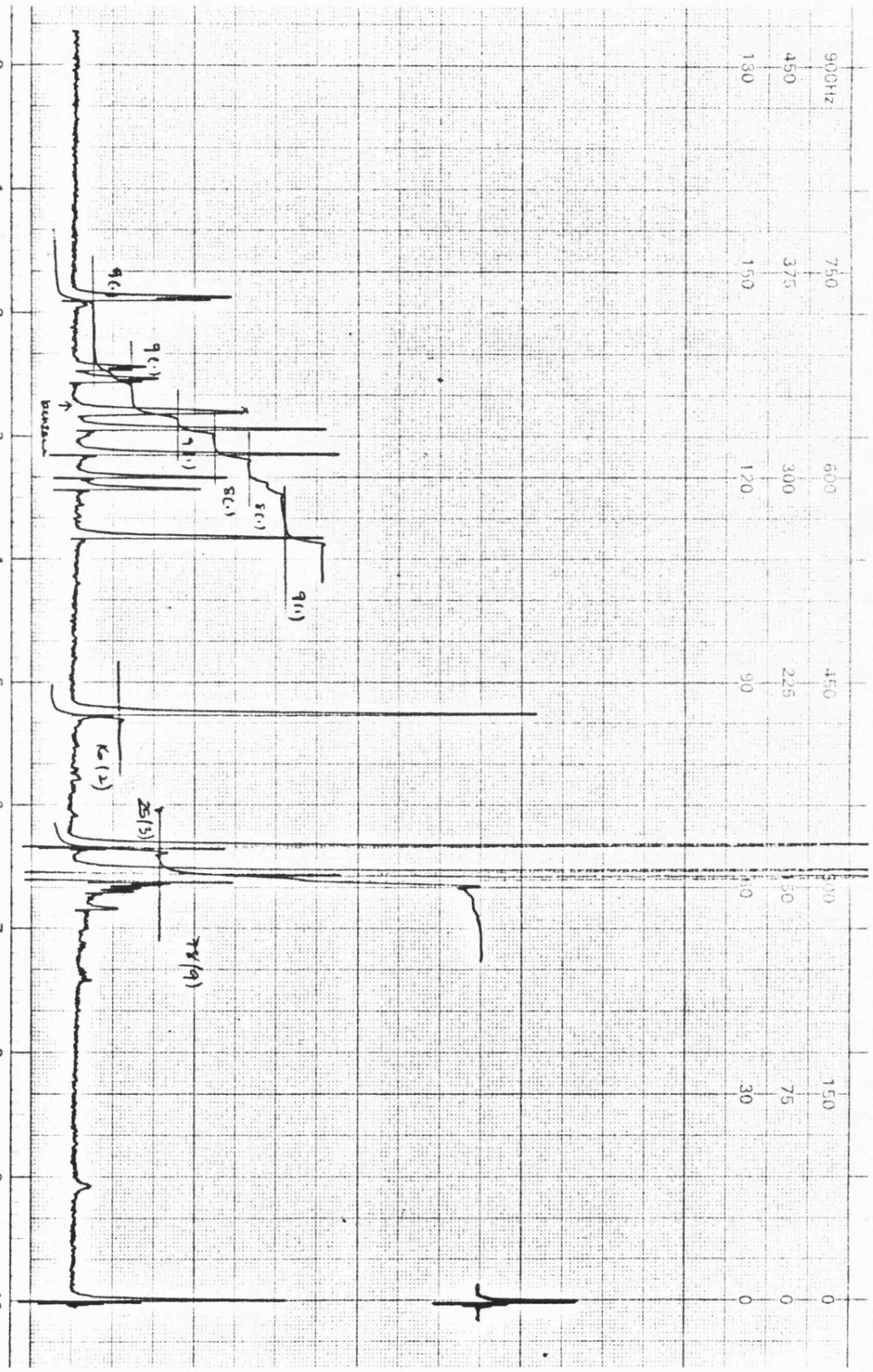
[E]4-(3,4-Dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone $CDCl_3$



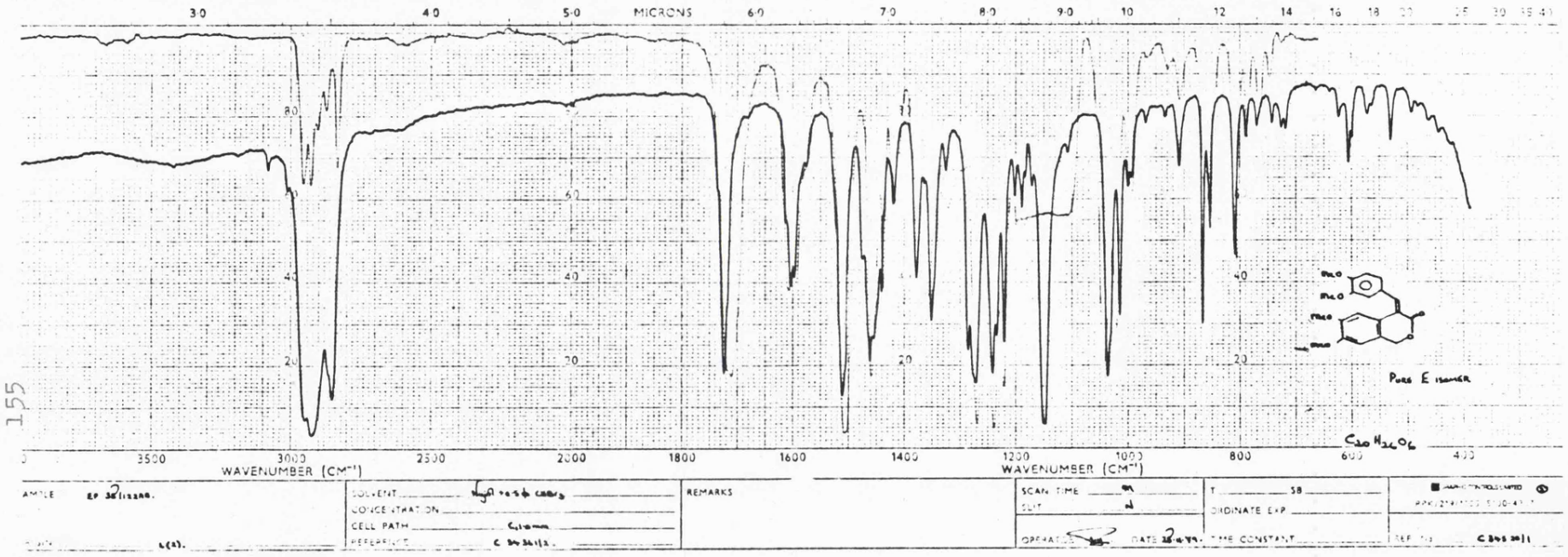
[Z]-4-(3,4-Dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone $CDCl_3$



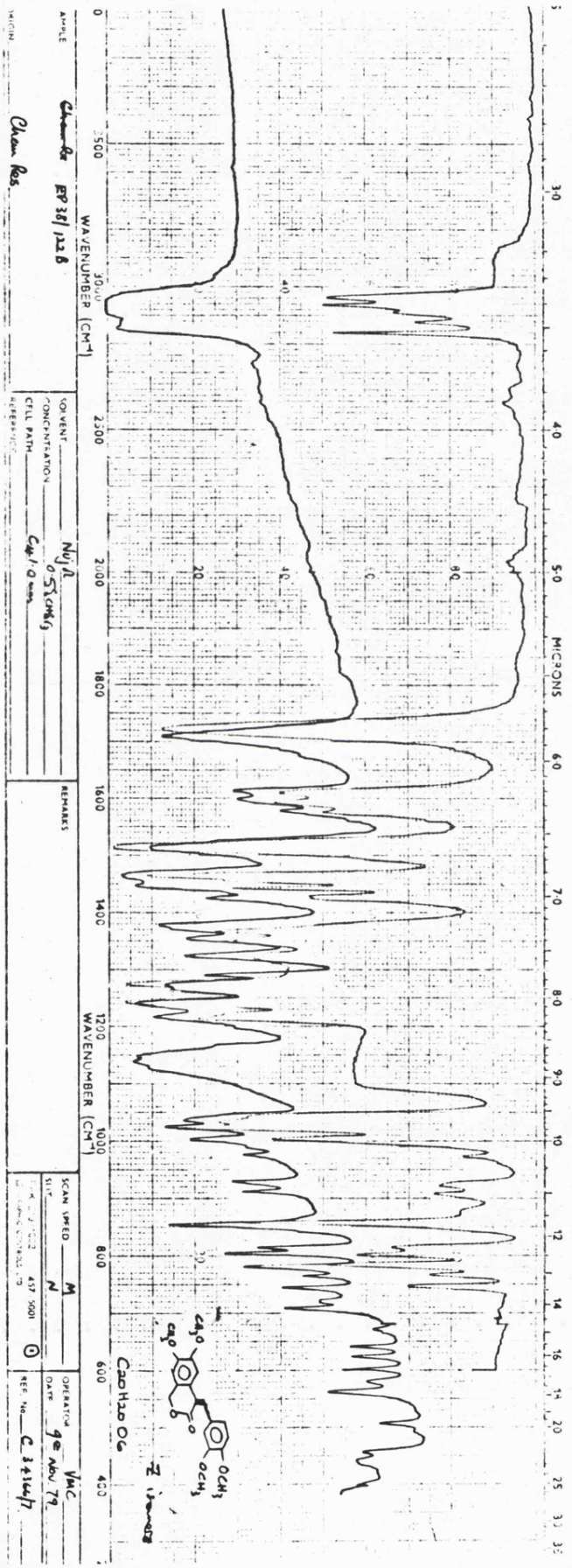
[E]4-(3,4-Dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone C_6D_6



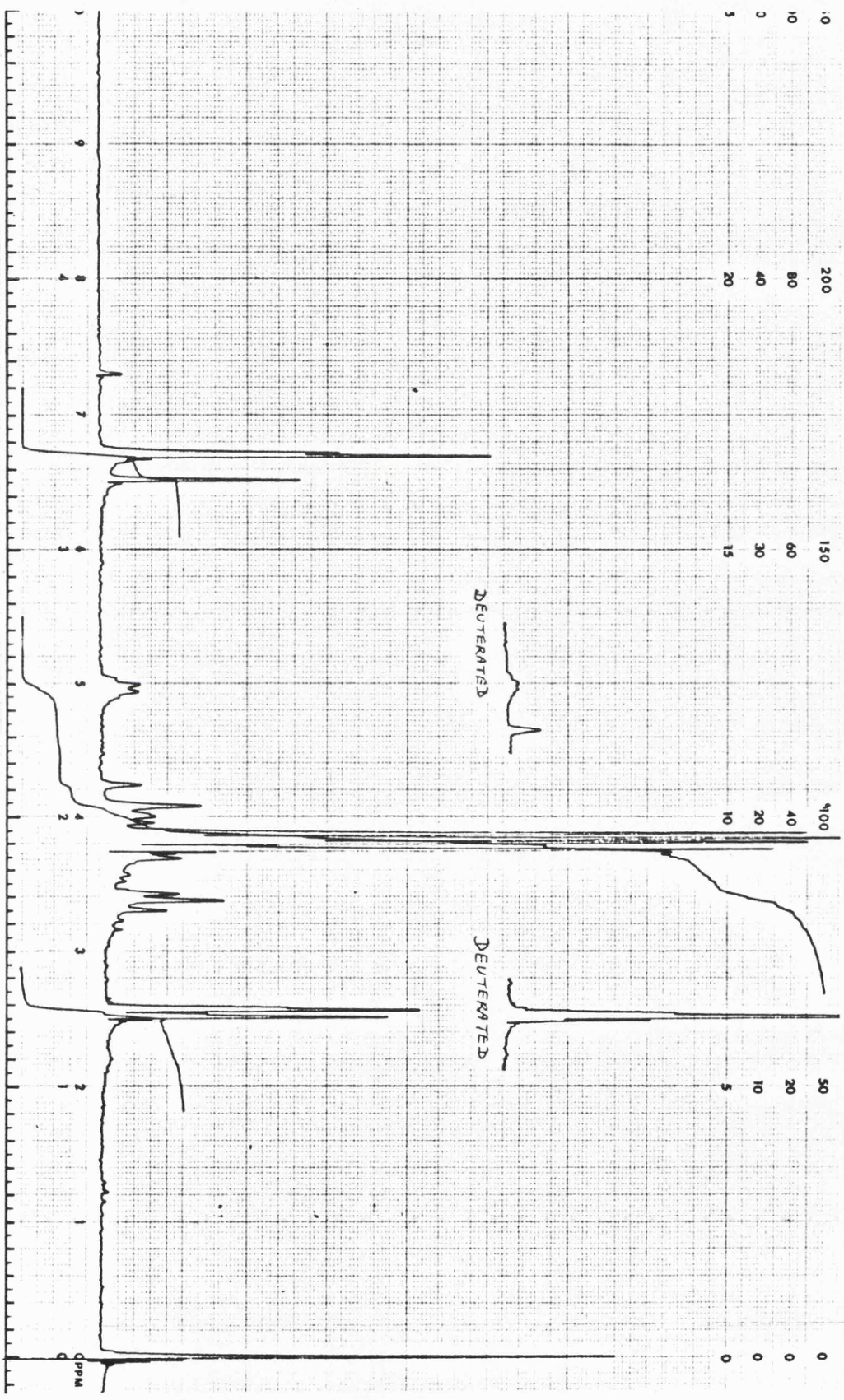
[2]4-(3,4-Dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone C_6D_6



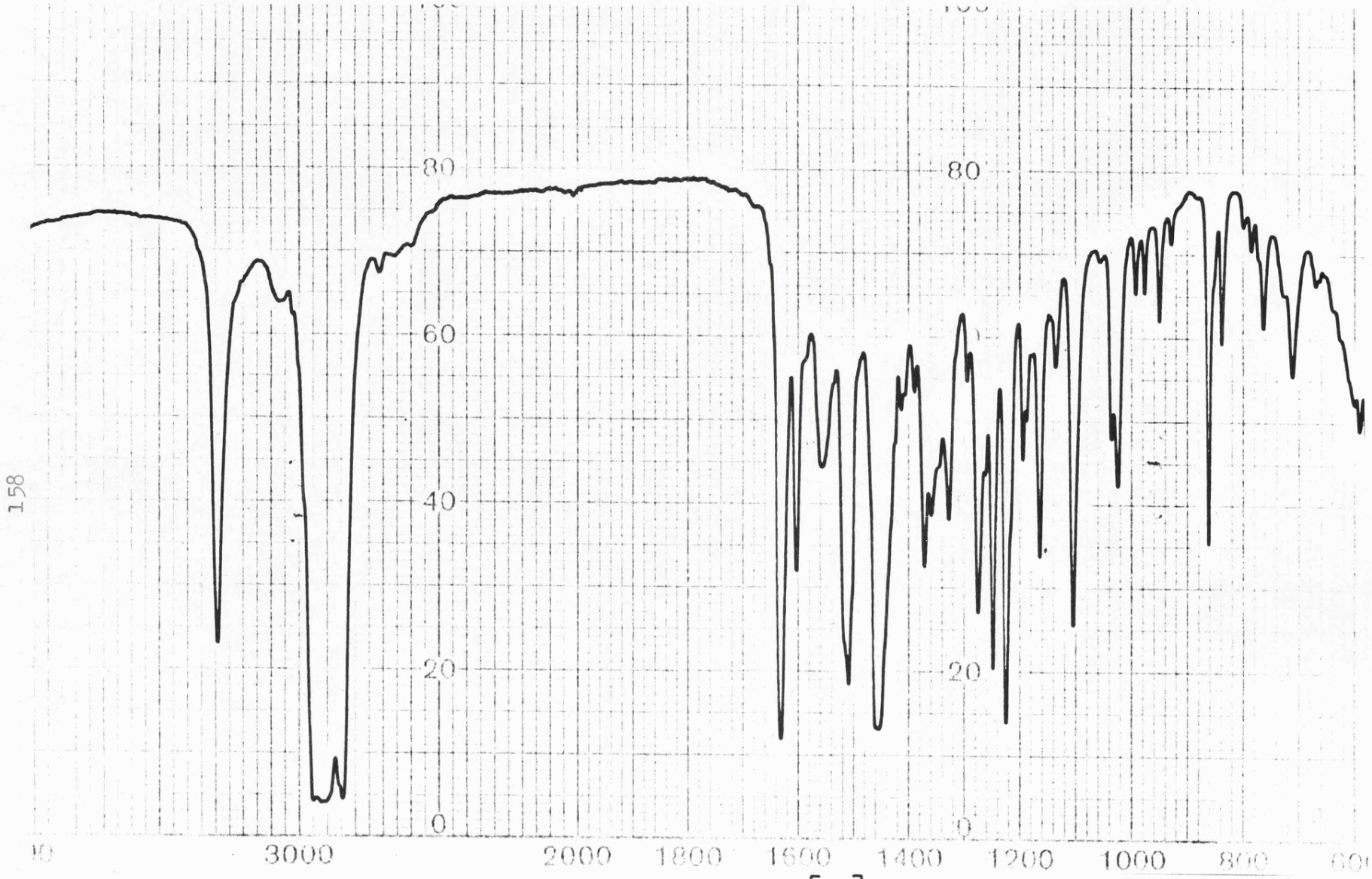
[E] 4-(3,4-Dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone



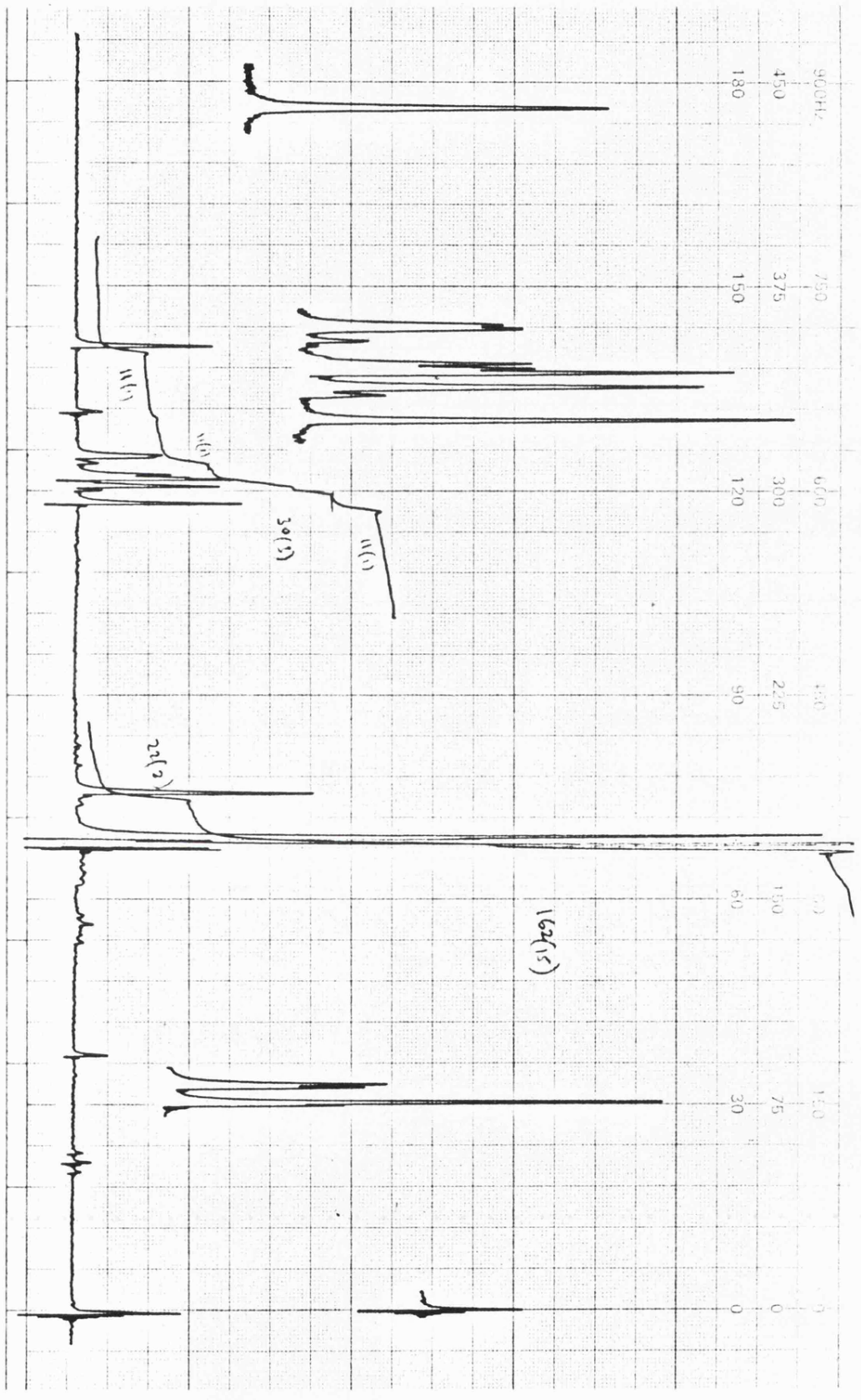
[2]4-(3,4-Dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone



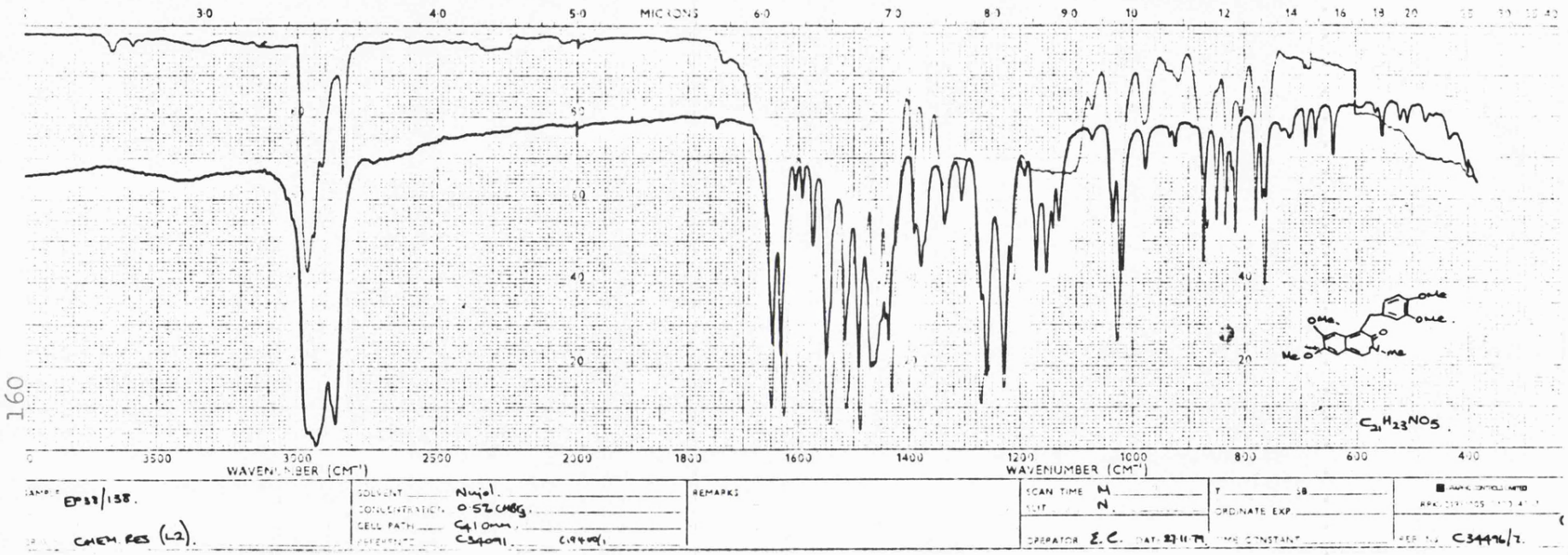
2,3,8,9-Tetramethoxy-5-(N-methylformamido)-dibenzo[b,f]cycloheptane



2,3,8,9-Tetramethoxy-5-(N-methylformamido)-dibenzo[b,f]cycloheptane

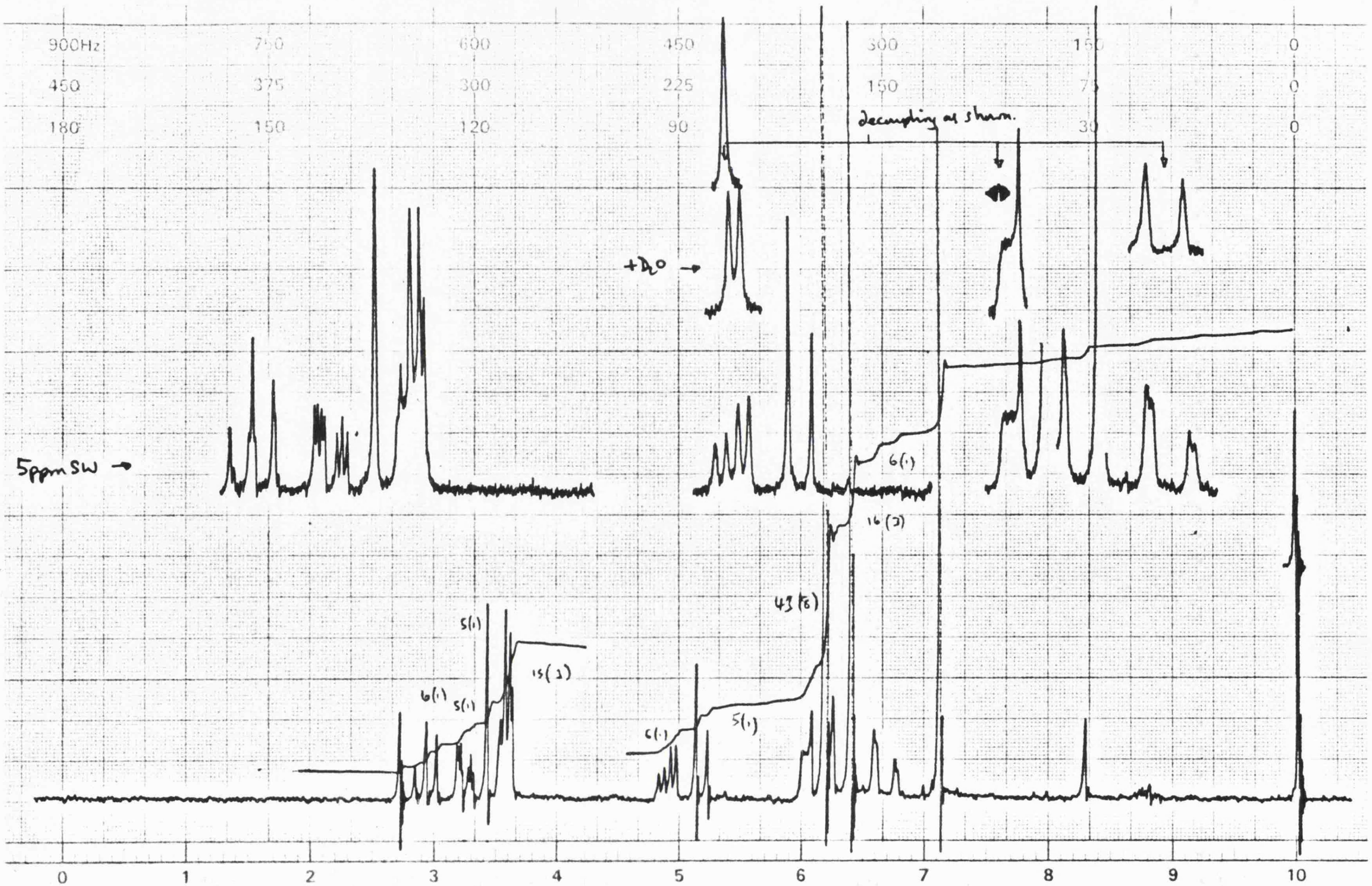


6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)-2-methyl-3(2H)-isoquinolinone

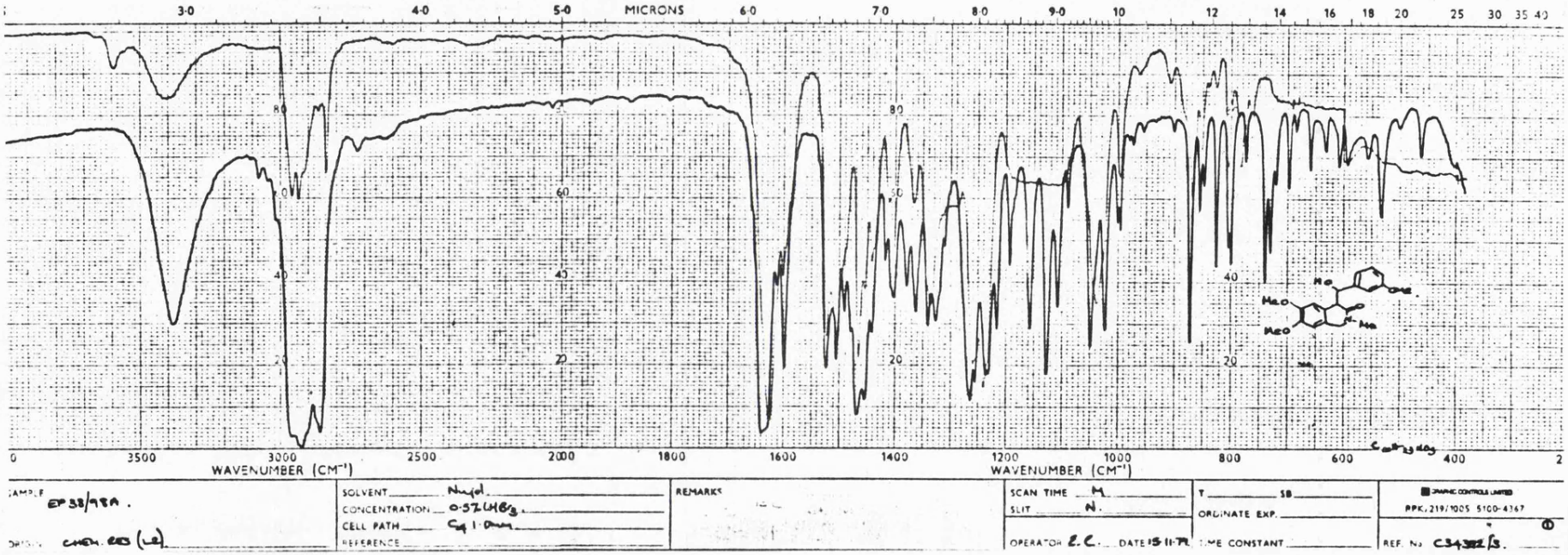


160

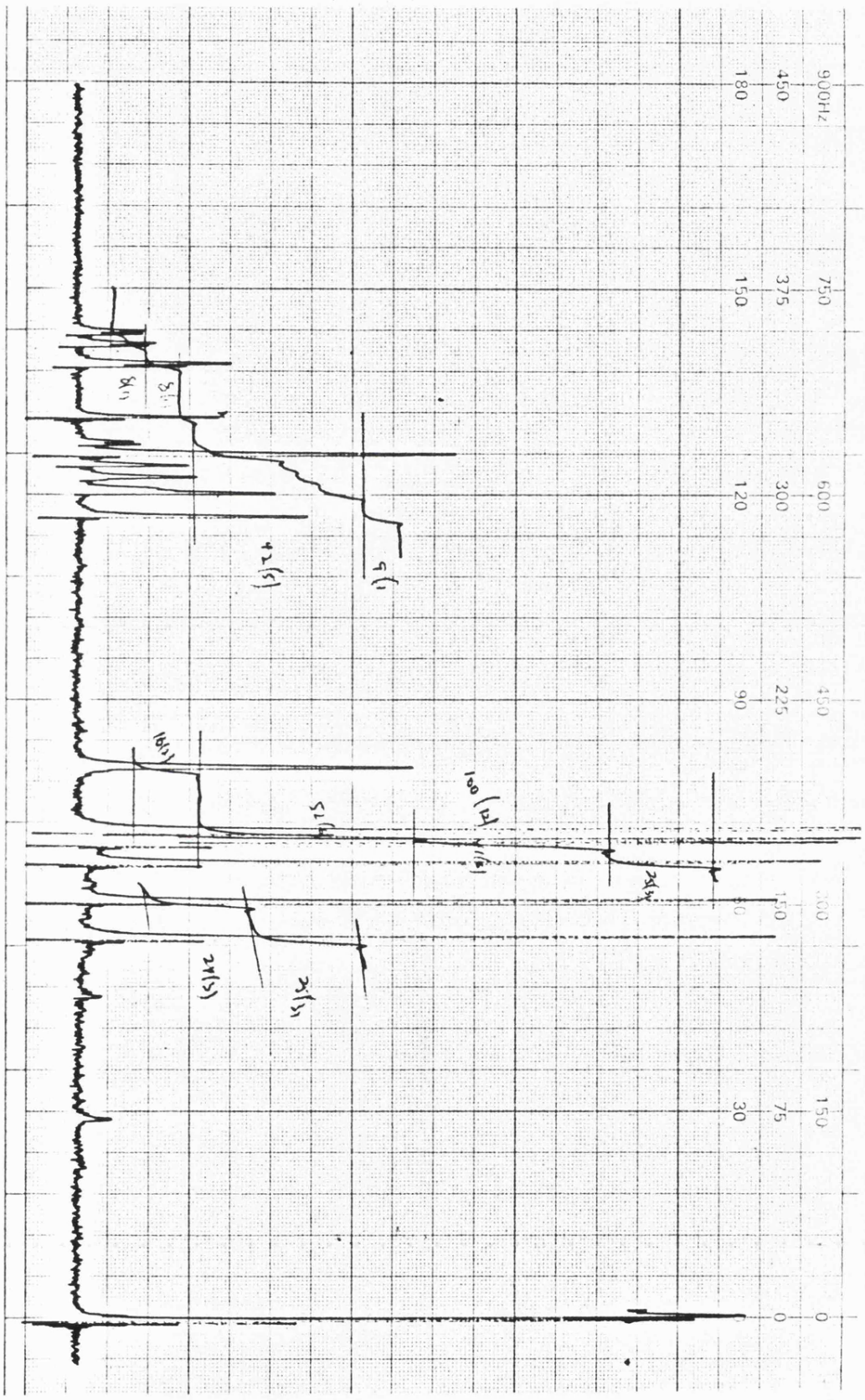
6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)-2-methyl-3(2H)-isoquinolinone



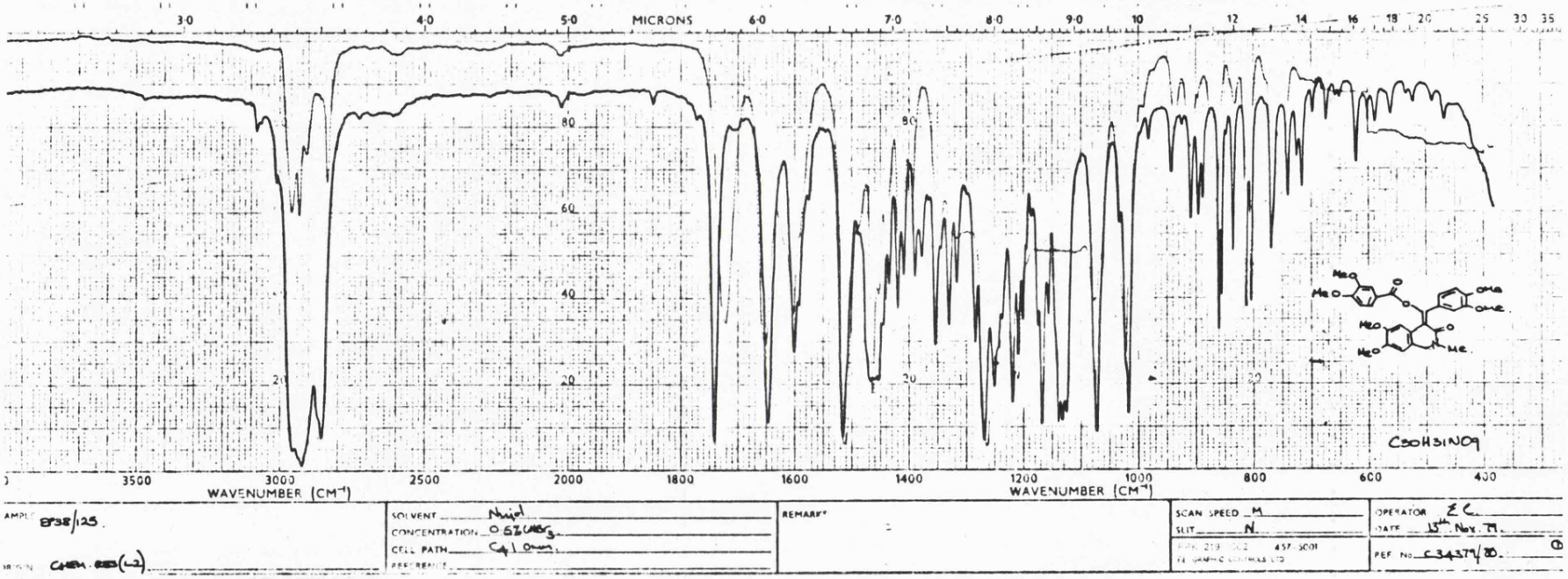
1,4-Dihydro-4-(α-hydroxy-3-methoxybenzyl)-6,7-dimethoxy-2-methyl-3(2H)-isoquinolinone



1,4-Dihydro-4-(α-hydroxy-3-methoxybenzyl)-6,7-dimethoxy-2-methyl-3(2H)-isoquinolinone

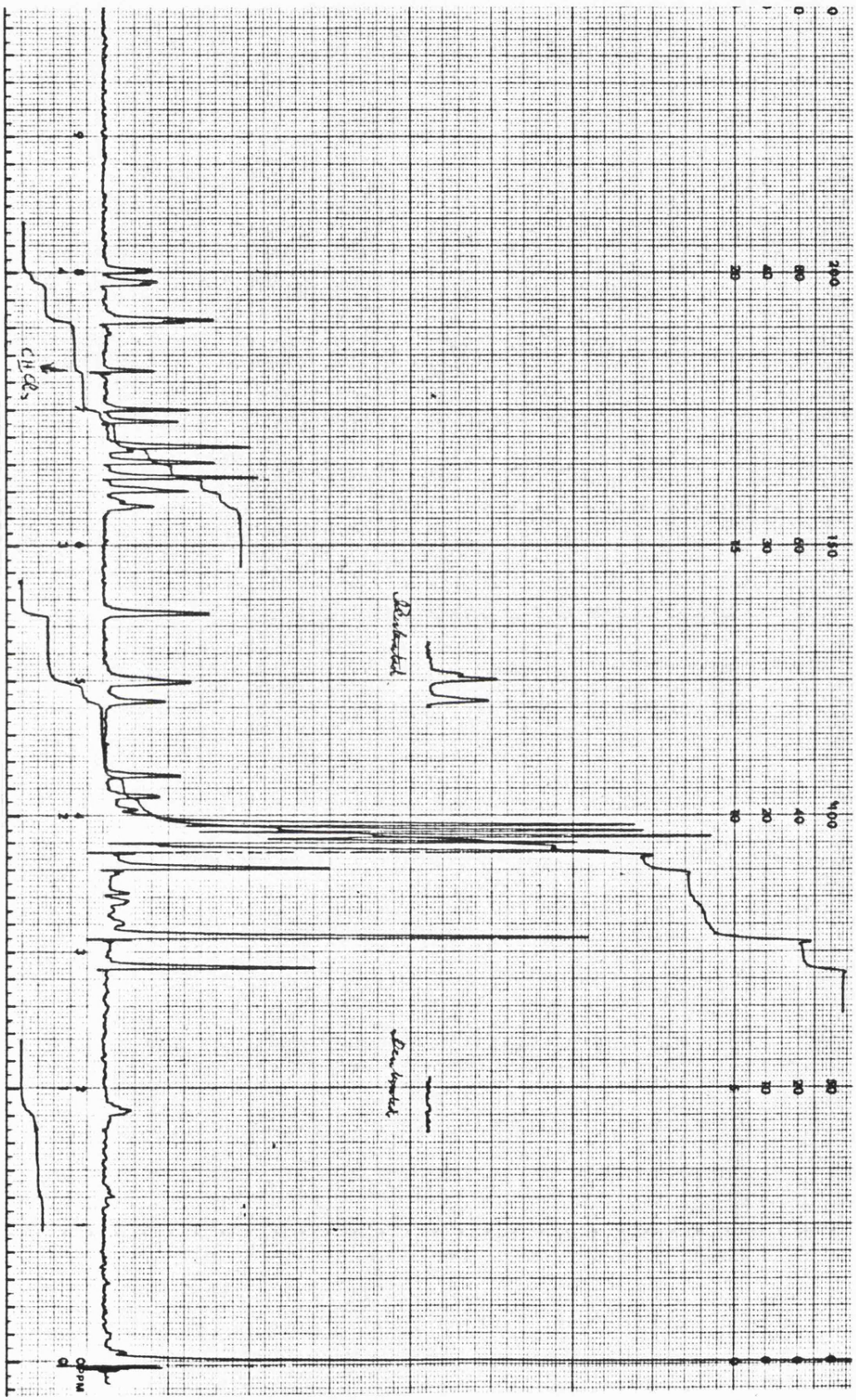


1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxy-α-(3,4-dimethoxybenzoyloxy)benzylidene)-2-methyl-3(2H)-isoquinolinone

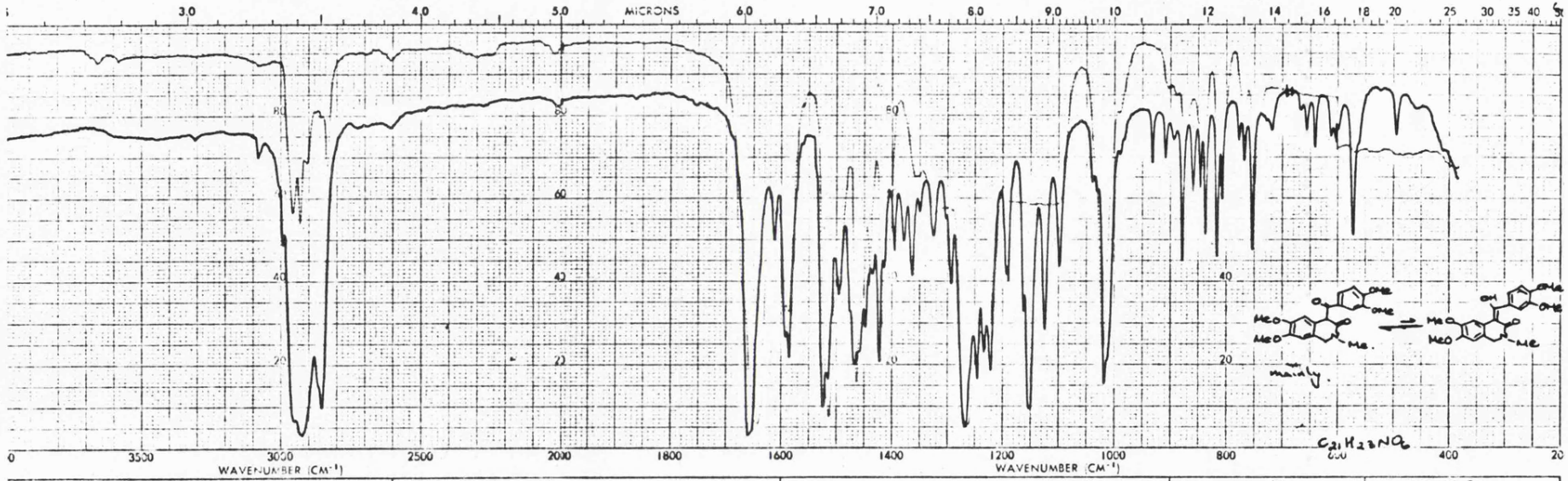


1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxy-α-(3,4-dimethoxybenzoyloxy)benzylidene)

-2-methyl-3(2H)-isoquinolinone



1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzoyl)-2-methyl-3(2H)-isoquinolirone



SAMPLE EP38/99.

ORIGIN CHEM. RES (CW).

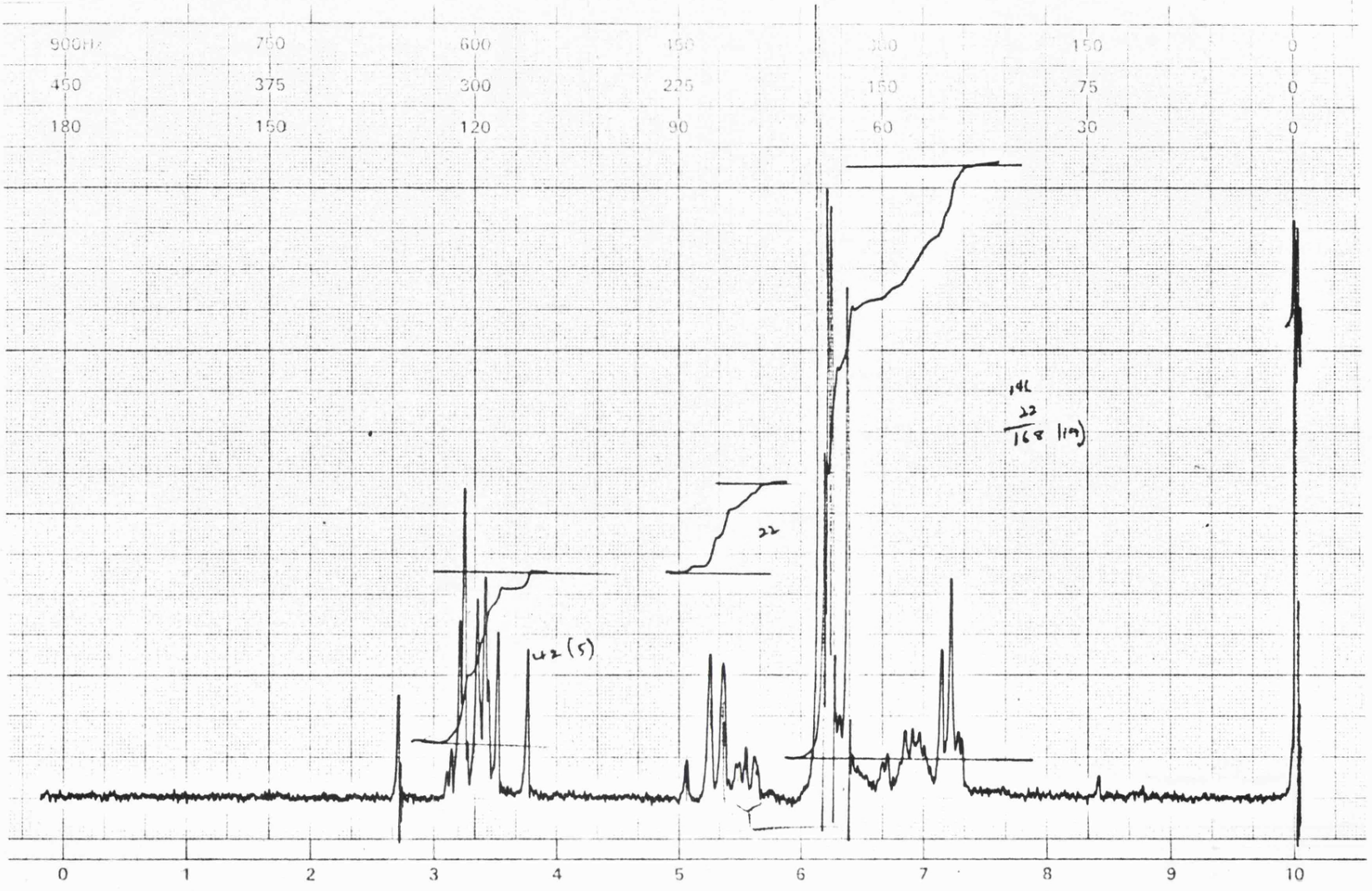
SOLVENT Nujol.
CONCENTRATION 0·5% CHCl3.
CELL PATH CaF2 Disc.
REFERENCE

REMARKS

SCAN MODE M
SLIT N. TIME CONSTANT
PART No 457 - 5133

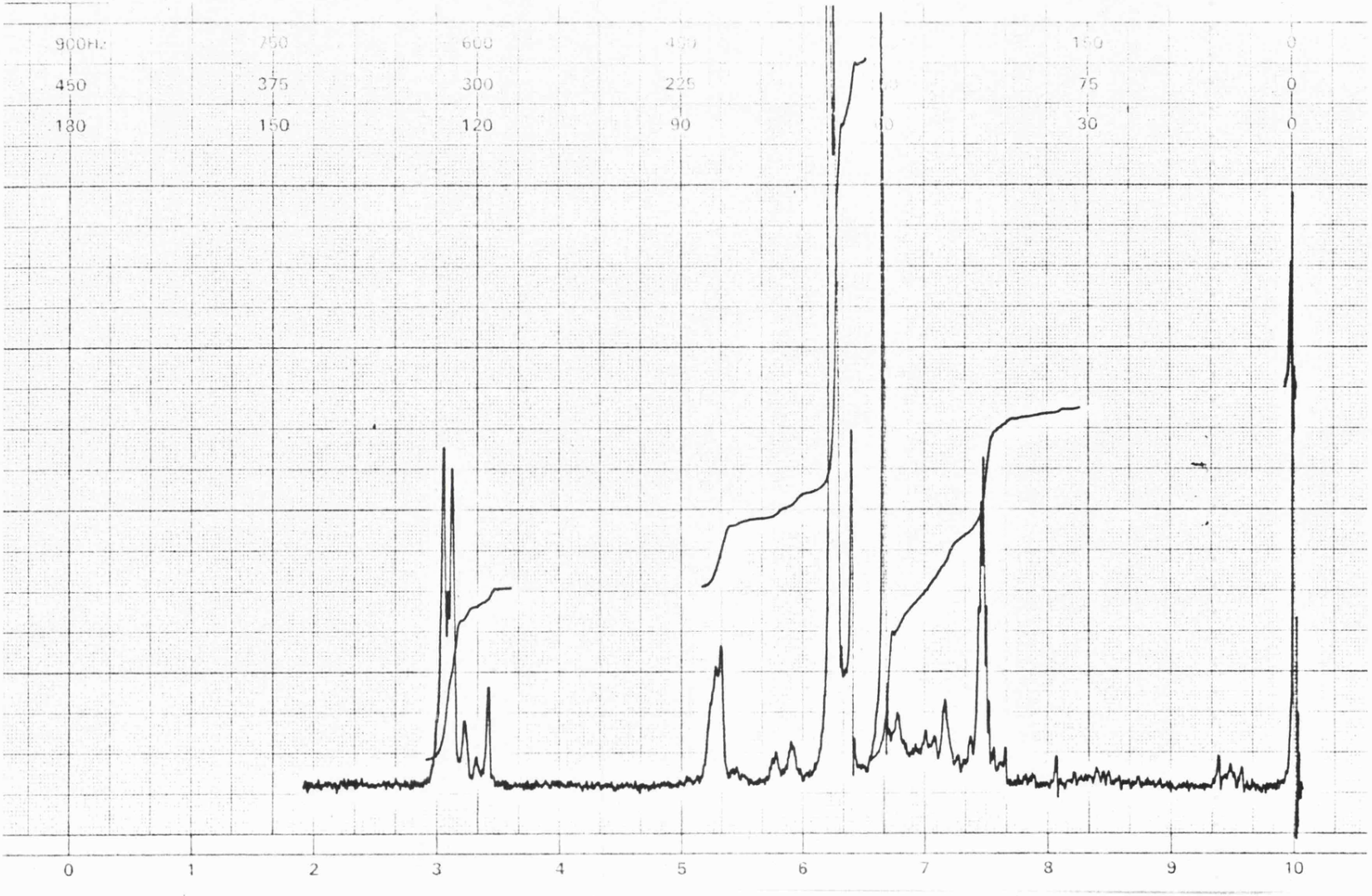
OPERATOR E.C.
DATE 4th Oct. 79.
REF. No C34107/8. (1)

1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzoyl)-2-methyl-3(2H)-isoquinolinone



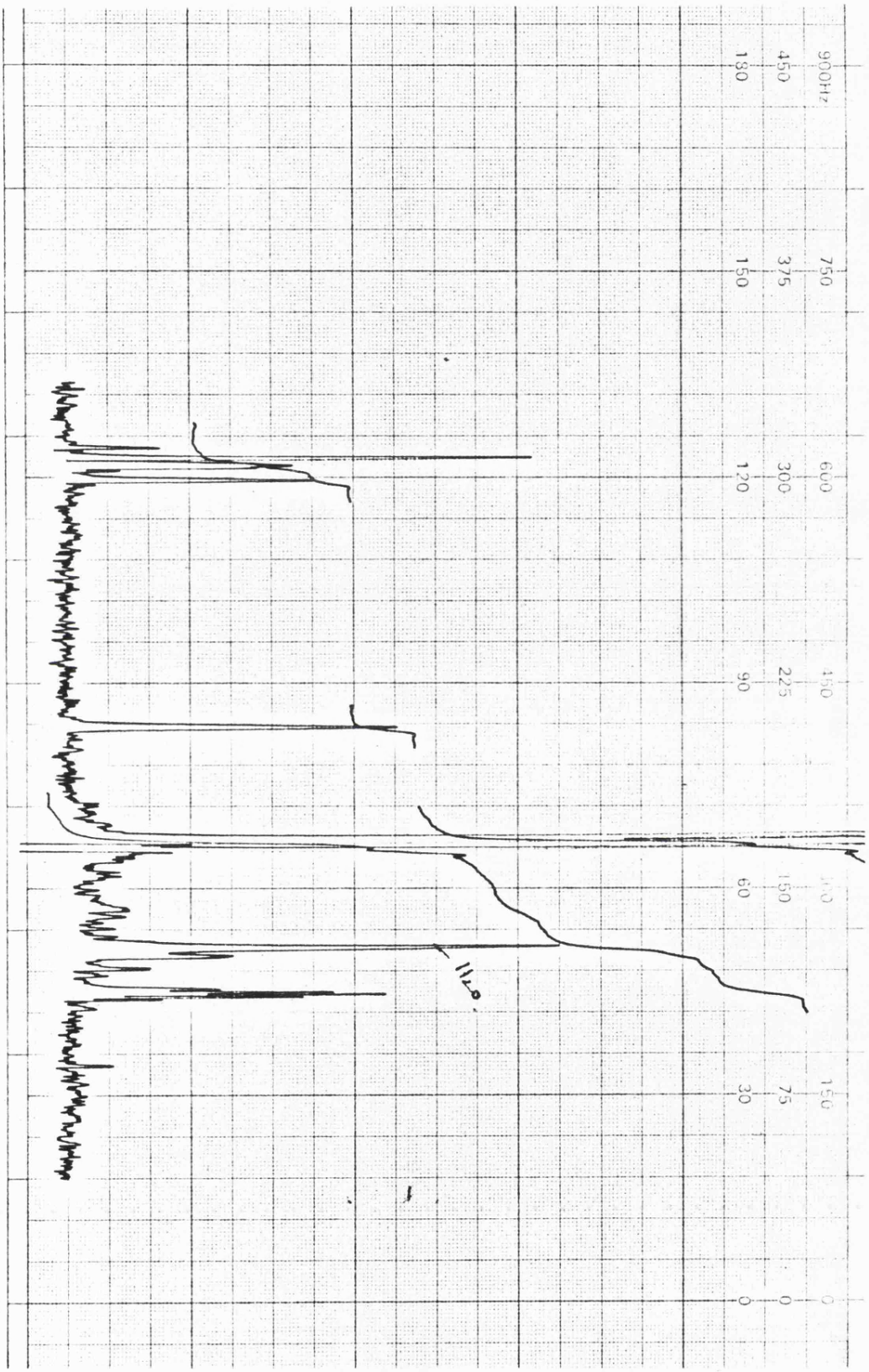
2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline

$CDCl_3$



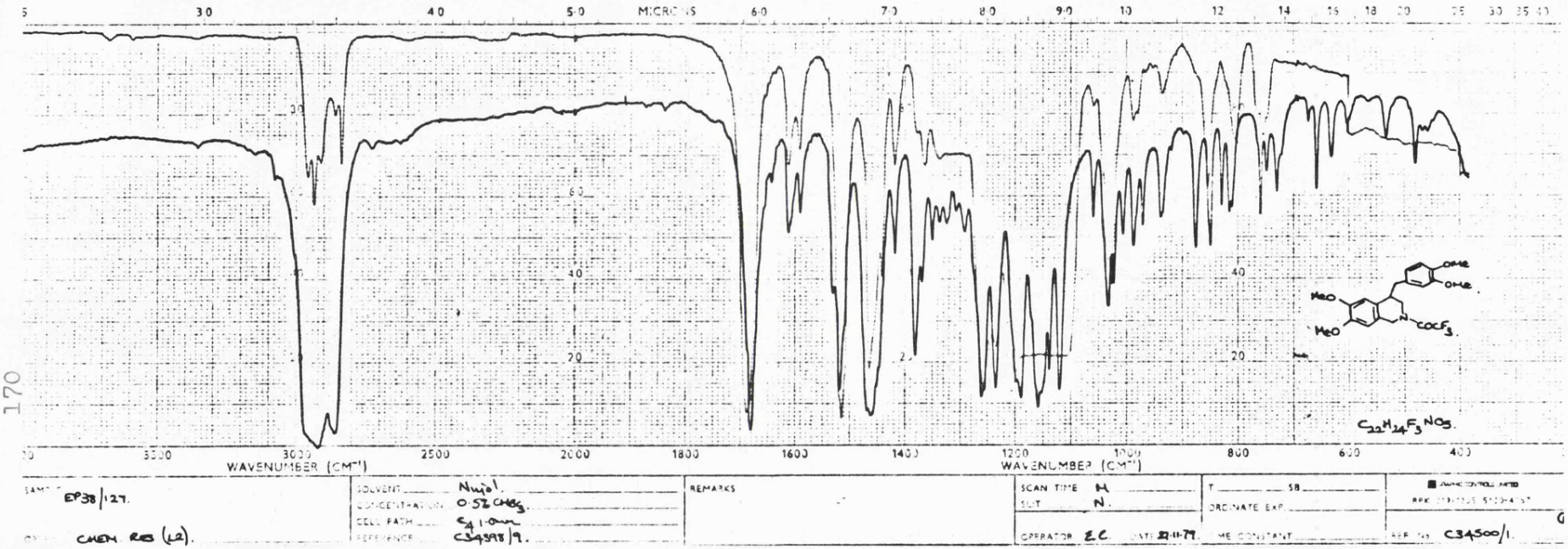
2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline

$(CD_3)_2SO$ at 35°C



2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline

$(CD_3)_2SO$ at 110°C



2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline

CYCLIC VOLTAMMOGRAMS

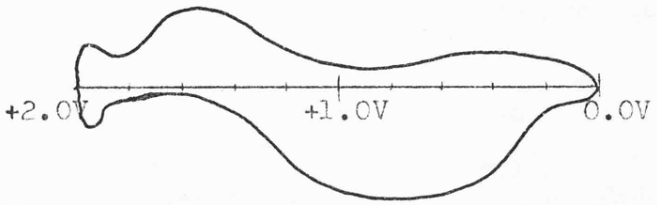


fig. 3

1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-methoxybenzyl)-2-methylisoquinoline in 0.1M $NaClO_4$ in acetonitrile.

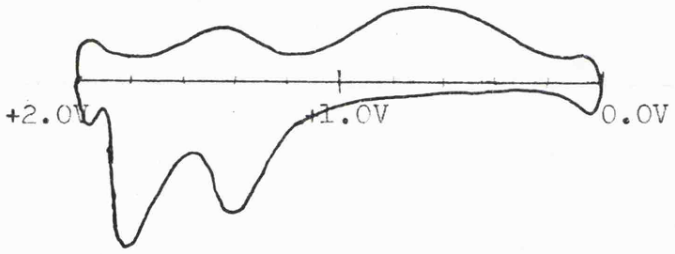


fig. 4

1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-methoxybenzyl)-2-methylisoquinoline in 0.1M tetrabutylammonium tetrafluoroborate in trifluoroacetic acid:dichloromethane, 1:4.

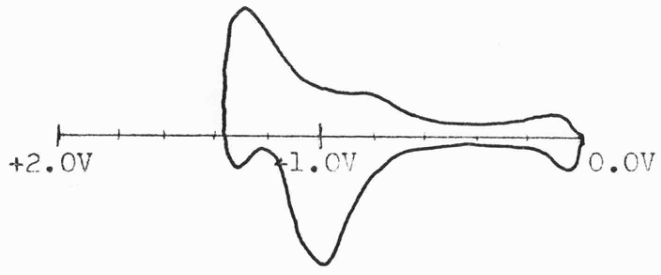


fig. 5

2-trifluoroacetyl 1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline in 0.1M $NaClO_4$ in acetonitrile.

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